RESISTANT ASCITES TREATED BY COMBINED DIURETIC THERAPY
(SPIRONOLACTONE, MANNITOL, AND CHLOROTHIAZIDE)

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THE mechanism of renal salt and water retention associated with the formation of ascites in patients with hepatic cirrhosis seems to involve both proximal and distal renal tubules. An important feature is the increased production of aldosterone, or the reduced rate of its inactivation by the liver (Peterson 1959, Ulick 1959), which increases sodium retention and potassium loss at the level of the distal renal tubule (Wilde et al. 1959). This aspect can be treated by giving aldosterone antagonists, of which the spirolactones are the best available (Cella and Kagawa 1957, Liddle 1958). Although sometimes effective in ascites and cirrhosis, Kerr et al. (1958) noted an unsatisfactory diuresis with an intramuscular spirolactone, SC 8109, in three cirrhotic patients with ascites. This may be explained by postulating increased proximal tubular reabsorption of sodium and water, so that too little sodium reaches the distal tubule, where the anti-aldosterone action of spirolactones would prevent sodium reabsorption. It seemed desirable, therefore, to combine the spirolactones with chlorothiazide, a diuretic which acts primarily on the proximal renal tubular reabsorption of sodium (Vander et al. 1959). A double action would thus be produced on the renal tubule. Sodium not reabsorbed in the proximal tubule due to the effect of chlorothiazide would pass to the distal tubule where it would remain unabsorbed due to the aldosterone antagonist; hence it would reach the urine (fig. 1).

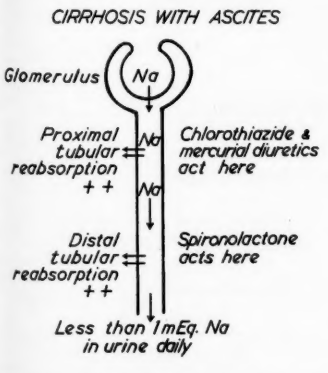

Fig. 1—Renal tubular reabsorption of sodium in cirrhosis with ascites.

Avid sodium retention is probably due to increased proximal and distal tubular reabsorption of sodium. Chlorothiazide and mercurial diuretics are thought to inhibit proximal sodium reabsorption whereas spironolactone acts by inhibiting the action of aldosterone on the distal tubule.

Mannitol was used as an osmotic diuretic to increase the filtered load of sodium and water reaching the distal tubule, so permitting the aldosterone antagonist to be more effective. Mannitol also increases the volume of water excreted in relation to solutes ("free water" clearance) in cirrhosis (Schedl and Bartter 1958).

We have used spironolactone (SC-9420, 'Aldactone'), a thioacetic acid derivative of the steroid-17-spirolactone series, which is the most potent oral aldosterone antagonist available (Gantt and Dyniewicz 1959). We tested the diuretic action of this substance alone and in combination with mannitol and chlorothiazide in cirrhotic patients with resistant ascites.

Read et al. (1959) found that chlorothiazide, although an effective diuretic, produced hepatic coma in certain patients with liver disease. This was attributed to excessive potassium loss associated with alkalosis; and the frequency of hepatic coma was reduced by giving potassium supplements. Because spirolactones inhibit urinary potassium loss they might prevent the potassium depletion and consequent hepatic coma. We also noted the effect of the drug combination on the neuropsychiatric state of the patients.

The Investigation

Patients Studied

Eight patients with portal cirrhosis, and one with biliary cirrhosis, were studied (table I).

TABLE I—PATIENTS STUDIED

Case no.	Sex	Age (yr.)	Ætiological factor	Duration of ascites (mos.)	Previous treatment
1	M	62	Unknown	8	Low-Na diet; chlorothiazide; mersalyl; paracentesis × 10
2	F	44	Primary biliary	8	Low-Na diet; mersalyl
3	F	31	Post-hepatitis	14	Low-Na diet; chlorothiazide; paracentesis × 30
4	M	43	Alcoholism	16	Low-Na diet; chlorothiazide; paracentesis × 6
5	F	72	Unknown	13	Low-Na diet; chlorothiazide; mersalyl; paracentesis × 4
6	M	34	Unknown	10	Low-Na diet; chlorothiazide; mersalyl; paracentesis × 5
7	F	38	Post-hepatitis	14	Low-Na diet; chlorothiazide; paracentesis × 3
8	F	17	Post-hepatitis	15	Low-Na diet; chlorothiazide; mersalyl; paracentesis × 3
9	F	56	Unknown	10	Low-Na diet; chlorothiazide; paracentesis × 3

All the patients had tense ascites which had persisted for 8–16 months (mean 12 months), and four had gross peripheral œdema. The ascites had proved refractory to rest in bed, dietary sodium restriction (22 mEq. per day), and mercurial diuretics or chlorothiazide. All the patients had required paracentesis several times. Their serum-albumin levels were 2·5 g. per 100 ml. or less. All the patients had portal hypertension, shown by splenomegaly, radiological evidence of œsophageal varices, and a raised intrasplenic pressure. Cases 2 and 6 had previously been in hepatic coma.

Methods

The patients received daily 22 mEq. sodium, 80 mEq. potassium, and 80 g. protein (except cases 2 and 6, which received 40 g. protein). Fluid intake was measured but not restricted. The patients were weighed daily, and the urinary volume, sodium, potassium, and chloride were estimated 24-hourly. The serum sodium, potassium, chloride, and bicarbonate, and arterial ammonium levels (Seligson and Hirahara 1957) were estimated three times a week. Liver function (by routine tests) and blood-urea were estimated weekly. Electroencephalograms were analysed, slowing of the mean frequency indicating hepatic precoma (Laidlaw 1959).

Spironolactone 200 mg. was given twice daily by mouth, chlorothiazide 0·5 g. 6-hourly, and mannitol 200 g. as a 10% solution intravenously over a 6-hour period.

TABLE II—EFFECTS OF CHLOROTHIAZIDE AND SPIRONOLACTONE, ALONE AND COMBINED WITH MANNITOL, ON URINARY VOLUME, ELECTROLYTE CONTENT, AND BODY-WEIGHT
(The results are the mean of a 5-day collection)

Case no.	Control period (mean of 5 days)			Chlorothiazide (mean of 5 days)				Spironolactone (mean of 5 days)				Spironolactone and mannitol (mean of 5 days)				Spironolactone and chlorothiazide (mean of 5 days)				Spironolactone, chlorothiazide, and mannitol (mean of 5 days)			
	Sodium (mEq. per 24 hr.)	Potassium (mEq. per 24 hr.)	Volume (ml. per 24 hr.)	Sodium (mEq. per 24 hr.)	Potassium (mEq. per 24 hr.)	Volume (ml. per 24 hr.)	Weight loss (kg.)	Sodium (mEq. per 24 hr.)	Potassium (mEq. per 24 hr.)	Volume (ml. per 24 hr.)	Weight loss (kg.)	Sodium (mEq. per 24 hr.)	Potassium (mEq. per 24 hr.)	Volume (ml. per 24 hr.)	Weight loss (kg.)	Sodium (mEq. per 24 hr.)	Potassium (mEq. per 24 hr.)	Volume (ml. per 24 hr.)	Weight loss (kg.)	Sodium (mEq. per 24 hr.)	Potassium (mEq. per 24 hr.)	Volume (ml. per 24 hr.)	Weight loss (kg.)
1	16	61	1020	17·5	94	1310	0	106	54	1510	3	149	57	2530	4	130	71	1810	4	..	..	..	..
2	3	49	930	4·1	82	1130	0	30	45	1220	1	71	43	2130	2	161	69	2130	5	..	..	..	..
3	0·7	63	1110	0·9	105	1410	0	7·5	50	1140	0	81	54	2420	3	131	73	2230	4	115	55	3010	4
4*	0·5	41	820	1·2	83	1010	0	6·4	35	840	0	15	38	1130	0	60	62	1430	2	111	51	2930	5
5*	0·8	37	900	1·3	105	1150	0	3·5	36	890	0	5	35	1140	0	55	50	1510	2	80	43	2280	4
6	0·9	28	600	0·8	74	950	0	1·2	26	580	0	7·2	28	910	0	21	39	1230	0	39	35	2150	2
7	1·3	42	830	15·7	73	1230	0	21	44	1120	1	73	45	2350	3	52	51	1530	1	101	43	3030	6
8*	1·1	31	720	2·1	95	1050	0	7·4	33	810	0	84	35	2270	3	62	40	1570	1	104	38	2470	4
9*	0·9	25	650	1·3	72	830	0	2·8	25	800	0	61	33	1860	2	..	..	..	..	124	45	2380	4

*These patients had a second course of spironolactone, chlorothiazide, and mannitol.

During the control period of 5 days the patients had a constant diet. The following combinations of diuretics were used (fig. 2):

1. Chlorothiazide for 3 days.
2. Spironolactone for 3 days.
3. Mannitol infusion.
4. Spironolactone, with mannitol on the 2nd day.
5. Spironolactone and chlorothiazide for 3 days.
6. Spironolactone for 3 days, with mannitol on the 2nd day, and chlorothiazide on the 2nd and 3rd days.

All the patients had reverted to their pretreatment state as judged by urinary sodium and potassium levels, before a new combination was used.

Results

Control period.—The basal level of urinary sodium excretion was less than 1 mEq. daily except in three patients (cases 1, 2, and 7); urinary potassium levels varied from 25 to 61 mEq. per 24 hours; and urine-volumes ranged from 600 to 1100 ml. per day (table II, fig. 2). Under these conditions the gain in weight was very slight in all the patients except one (case 6) in whom, after a recent paracentesis, ascites was reaccumulating despite sodium restriction. None of the patients was at the terminal stage of liver failure (Hecker and Sherlock 1956) when the trial was started. They were all very emaciated and had various degrees of abdominal discomfort from the tense ascites.

Spironolactone.—The mean 24-hour urinary sodium excretion rose in all patients whilst urinary potassium loss was reduced (fig. 2). This effect was not noted until 24 hours after spironolactone was started, but it persisted for 48–72 hours after the drug was discontinued (fig. 3). In view of this prolonged action, the urinary electrolyte excretions are expressed as a mean of five daily collections. In only three patients (cases 1, 2, and 7—i.e., those with the higher basal sodium excretions) was the ascites affected clinically, as shown by reduction in weight and increase in urine-volume (table II). Serum-potassium levels rose slightly in all patients. Serum-sodium levels were unaltered, except in three patients, where striking natriuresis was associated with reduction in serum-sodium levels (table III).

Mannitol.—A 6-hour intravenous infusion of mannitol resulted in an increase of mean urine-volume over 3 days, even allowing for the 2 litres infused. Urinary sodium levels were not affected, but potassium excretion rose slightly (fig. 2). Creatinine-clearance was unchanged in one patient (case 8). Clinically the patients' condition was unaltered.

Spironolactone and mannitol.—Addition of mannitol on the 2nd day of the 3-day course of spironolactone produced a dramatic diuresis with loss of weight on six out of nine occasions (table II, fig. 3). For the whole group the urinary sodium level increased more than 100% over that achieved with spironolactone alone, while the urinary potassium excretion did not increase significantly (fig. 2). In three patients (cases 3, 8, and 9) urinary sodium loss increased tenfold over that produced by spironolactone alone (table II). Serum-potassium levels were unaltered, but serum-sodium levels rose significantly in the six

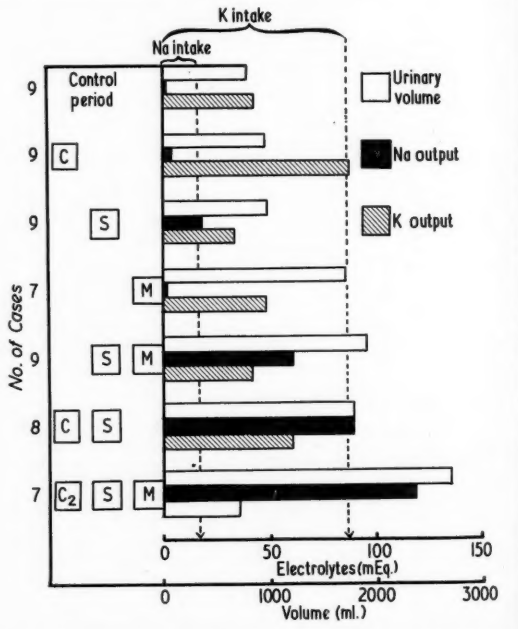

Fig. 2—Mean 24-hour urinary volume, and sodium and potassium output in patients with cirrhosis and resistant ascites during treatment with spironolactone (S) 400 mg. daily for 3 days; mannitol (M) 2 litres of 10% solution intravenously over 6 hours alone or on the 2nd of a 3-day course; and chlorothiazide (C) 2 g. daily for 3 days, or (C_2) 2 g. daily on the 2nd and 3rd days of a 3-day course alone and in combination.

The means for each patient were derived from a 5-day collection starting with each new combination of drugs, except in the case of mannitol where the means were from a 3-day collection.

TABLE III—CHANGES IN SERUM SODIUM AND POTASSIUM LEVELS (IN MEQ. PER LITRE) AFTER 3-DAY COURSES OF CHLOROTHIAZIDE AND SPIRONOLACTONE ALONE AND COMBINED WITH MANNITOL

Case no.	Control		Chlorothiazide		Spironolactone		Spironolactone and mannitol		Spironolactone and chlorothiazide		Spironolactone, chlorothiazide,* and mannitol	
	Sodium	Potassium	Sodium	Potassium	Sodium	Potassium	Sodium	Potassium	Sodium	Potassium	Sodium	Potassium
1	131	3·7	−3	−0·9	−3	+0·2	+7	−0·1	−6	−0·2	..	..
2	130	3·5	−6	−1·0	−4	+0·1	+11	+0·1	−11	−0·2	..	..
3	133	3·8	−2	−0·7	−1	−0·1	+10	−0·1	−9	−0·3	+12	+0·2
4	127	3·4	+1	−0·5	+1	+0·1	+2	0	−7	−0·1	+5	+0·4
5	128	2·9	0	−0·3	−1	+0·2	+3	−0·1	−4	−0·2	+5	+0·4
6	125	2·9	−1	−0·6	−1	+0·1	+1	−0·1	0	−0·1	+6	+0·1
7	137	3·4	+1	−0·7	−4	+0·1	+8	0	−7	−0·1	+7	−0·1
8	127	3·5	−1	−1·0	+1	+0·2	+8	−0·1	−6	−0·2	+9	+0·3
9	133	3·8	−1	−0·7	−1	+0·1	+8	−0·1	..	..	+9	+0·3

*Given on 2nd and 3rd days of the 3-day course only.

patients in whom a weight-losing diuresis was stimulated (table III). The mean urine-volume increased in these six patients by over 800 ml. per day compared with the effect of spironolactone alone, after the increased fluid intake with mannitol was taken into account (table II).

Chlorothiazide.—When given at the beginning of the trial, this diuretic produced an increase in potassium excretion (table II, fig. 2) with a fall in serum-potassium level, and it did not affect urinary sodium loss (table III). In two patients (cases 2 and 9) this effect was associated with clinical evidence of hepatic precoma, slow waves appearing in the electroencephalogram, and arterial ammonium and pH levels rising.

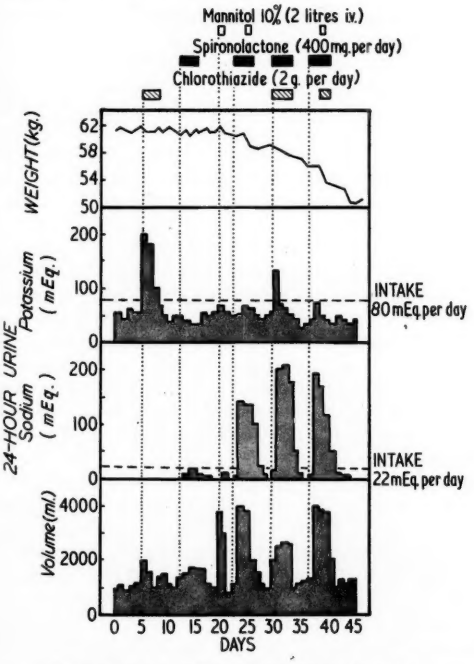

Fig. 3—Cirrhosis with resistant ascites (case 3).

During the control period urinary sodium was less than 1 mEq. per day, and it did not increase with chlorothiazide. Spironolactone produced a small natriuresis which began 24 hours after the drug was started, and persisted for 72 hours after it was stopped. The addition of mannitol produced a marked natriuresis with increase in urinary volume and weight loss. Chlorothiazide and spironolactone caused a greater loss of sodium than water, and hyponatræmia developed. Mannitol corrected the hyponatræmia and increased the water and sodium loss. The kaluretic effect of chlorothiazide was corrected by spironolactone after chlorothiazide was omitted on the 1st day of the course.

Chlorothiazide and spironolactone produced a considerable natriuresis seven out of eight times (table II), but this was always associated with a tendency to hyponatræmia (table III). Serum-potassium levels fell slightly, being related to the kaluresis the day before the spironolactone was effective (fig. 3). In case 2 hepatic precoma again developed and was associated with a sharp fall in serum-sodium as well as a reduction in serum-potassium levels (table III). Most patients felt weak and drowsy at the time of greatest diuresis. The loss of sodium in the urine was greater than that achieved with spironolactone and mannitol.

Chlorothiazide, spironolactone, and mannitol.—On all seven occasions this combination of drugs successfully promoted a diuresis, with consequent weight loss but without hyponatræmia or hypokalæmia (table III). Urine-volumes increased threefold over those of the control period; sodium loss increased but urinary sodium concentrations were not as high as those produced by spironolactone and chlorothiazide, and potassium loss was reduced (fig. 2). In all cases weight loss was greater when this combination of drugs was given (table II). Serum-sodium levels rose in all patients. Their appetites improved strikingly, and they had a general feeling of well being.

General Results

At the conclusion of the trial seven of the nine patients were completely free of ascites for the first time in over a year (table IV). They were up in the ward, and they felt extremely well. Their weight loss averaged 11 kg. A rise in serum-albumin level, averaging 0·6 g. per 100 ml., was associated with a slight increase in hæmatocrit (table IV). The other two patients (cases 5 and 6) were never satisfactorily controlled. In case 6 a diuresis was obtained only once, and this was not sustained; he later died following a large hæmorrhage from œsophageal varices.

Five of the seven patients who became free of ascites have since remained free from œdema for periods of 8–23 weeks without spironolactone; this has been associated with a fall in hæmatocrit and a further rise in serum-albumin of 0·7 g. per 100 ml. The other two patients (cases 4 and 8) reaccumulated ascites as outpatients (without spironolactone) and their serum-albumin levels fell.

Discussion

The ability of spironolactone to promote sodium loss whilst conserving potassium suggests that the drug acts by inhibiting aldosterone. This accords with the observations of Liddle (1958) on the mode of action of an earlier spirolactone SC 8109.

The failure to increase urinary sodium loss by the use of chlorothiazide, which acts on the proximal tubule,

TABLE IV—EFFECT OF DIURETICS ON SERUM-ALBUMIN, HÆMATOCRIT (P.C.V.), AND ASCITES

Case no.	Before treatment		At termination of spironolactone combination					Outpatient follow-up (without spironolactone)			Comment
	Albumin (g. per 100 ml.)	P.C.V. (%)	Duration (days)	Albumin (g. per 100 ml.)	P.C.V. (%)	Weight loss (kg.)	Ascites	Duration (wks.)	Albumin (g. per 100 ml.)	P.C.V. (%)	
1	2·1	44	42	3·1	47	11	None	23	4·0	38	Free of ascites on salt restriction only
2	2·2	45	44	3·0	46	8	None	23	3·7	37	Free of ascites on mersalyl and salt restriction
3	2·5	41	50	3·3	44	11	None	23	4·5	37	Free of ascites on chlorothiazide and salt restriction
4	2·5	45	60	3·2	47	14	None	15	2·9	44	Reaccumulated ascites after 6 weeks without spironolactone
5	2·2	44	120	2·3	46	4	Partially relieved	..	..	..	Died from bronchopneumonia whilst in hospital
6	2·5	44	102	2·3	47	0	Unchanged	..	..	..	Died from gastrointestinal hæmorrhage
7	2·4	46	65	3·5	46	14	None	15	4·5	39	Free of ascites on salt restriction
8	2·7	45	82	3·6	47	13	None	11	2·9	46	Reaccumulated ascites after 3 weeks without spironolactone
9	2·9	44	61	3·7	47	10	None	8	3·9	41	Free of ascites on salt restriction and chlorothiazide

suggests that sodium was reabsorbed in the distal tubule, probably under the influence of aldosterone. Conversely spironolactone had little effect on the patients who excreted less than 1 mEq. of sodium in the urine daily, suggesting that sodium was also reabsorbed proximal to the action of the aldosterone antagonist. The synergistic effect on sodium excretion obtained with mannitol, which acts proximally, or with chlorothiazide combined with spironolactone, might be explained by a simultaneous blockade of proximal and distal tubular sites of sodium reabsorption.

Hypokalæmia was effectively prevented by omitting chlorothiazide on the 1st day when there was little effect from spironolactone. The most effective combination of drugs for achieving natriuresis without hyponatræmia or hypokalæmia was spironolactone, chlorothiazide (for 2 days only), and mannitol.

Hyponatræmia tended to appear when spironolactone was combined with chlorothiazide. This suggests that relatively more sodium than water was excreted, and accords with the observations of Laragh et al. (1958) that chlorothiazide does not increase " free water " clearance. The combination of spironolactone with chlorothiazide appears to have accentuated the disturbance of water excretion in cirrhosis with ascites. One patient (case 2) developed hepatic precoma when given chlorothiazide and spironolactone, although the serum-potassium levels fell only slightly; the serum-sodium level, however, decreased from 135 to 124 mEq. per litre. Hyponatræmia has also appeared in patients who developed hepatic precoma when taking chlorothiazide (Read et al. 1958), and the hepatic coma which follows paracentesis is often associated with hyponatræmia (Nelson et al. 1951). A low serum-sodium level in the untreated patient with decompensated cirrhosis suggests a disturbance of water distribution between the intracellular and extracellular spaces, as total body-sodium in these patients is not reduced. Possibly diuretics, by producing a disproportionate loss of sodium in excess of water, accentuate this disturbance.

Prednisone will correct hyponatræmia in cirrhosis with ascites, promoting at the same time a water diuresis often unassociated with sodium (Stormont et al. 1959). Morrison and Chalmers (1959), using prednisone in combination with spironolactone and chlorothiazide, were able to prevent hyponatræmia. The mechanism of this action of prednisone is not understood, but it is not related to changes in aldosterone secretion, nor to alterations in glomerular filtration rate or antidiuretic hormone effect. Unfortunately fulminant infections often complicate the long-continued use of prednisone in these patients (Stormont et al. 1959).

Mannitol can achieve similar results when used with spironolactone and chlorothiazide. Osmotic diuretics may be as effective as steroids, and they do not encourage complicating infections. The action of mannitol in these patients does not seem to be related to changes in glomerular filtration rate because creatinine-clearance is unchanged. It probably reduces proximal tubular reabsorption of sodium and water; this may be greatly increased in cirrhosis with resistant ascites, and is responsible for hyponatræmia and reduced " free water clearance " (Schedl and Bartter 1958). The cause of increased proximal tubular reabsorption of sodium and water in such patients is not understood, but Schedl and Bartter (1958) suggest that it is independent of the effect of antidiuretic hormones, and our indirect evidence suggests that aldosterone is not concerned.

The beneficial effect of spironolactone in patients with cirrhosis and resistant ascites marks an important landmark in treatment. Adjuvant diuretic therapy is clearly essential, for aldosterone is only one factor in the maintenance of ascites. The most encouraging results were seen in patients in whom ascites did not reaccumulate when spironolactone therapy was stopped; in these the increase of plasma-volume was associated with a rise in serum-albumin levels. It would be extremely interesting to know whether the aldosterone secretion-rate had fallen in these patients, because the increase in their plasma-volumes may have reduced the stimulus to aldosterone production (Bartter et al. 1956). Continued freedom from ascites without the need for aldosterone antagonists suggests that hyperaldosteronism is no longer a major problem.

Summary

Nine patients with cirrhosis and resistant ascites were treated with an aldosterone antagonist spironolactone, alone and combined with chlorothiazide and mannitol. In seven cases ascites was cleared completely.

Spironolactone was more effective given in combination with chlorothiazide, but this often caused hyponatræmia. The addition of mannitol (an osmotic diuretic)

to the combination corrected the hyponatræmia and increased the natriuresis.

Thus resistant ascites may develop in cirrhosis when proximal tubular reabsorption of sodium becomes very high, and mannitol may reduce this tendency whilst increasing the volume of water excreted in relation to solutes (" free water " clearance).

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ROLE OF FUNDUS IN PREVENTION OF GASTRO-ŒSOPHAGEAL REGURGITATION

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THE mechanism which normally prevents reflux of gastric juice into the œsophagus and which becomes inefficient in the presence of a sliding hiatus hernia has never been satisfactorily demonstrated.

Allison (1948) described the pinchcock action of the diaphragm seen during œsophagoscopy. It was realised that this played little part in the prevention of regurgitation when it was shown that operations which interfered with the gastro-œsophageal junction, but which left the diaphragm unaltered—such as cardioplasties or œsophago-gastrostomies—were followed by œsophagitis in a high proportion of cases. Barium-swallow studies and manometric tracings of pressures in the œsophagus and stomach (Atkinson et al. 1957, Botha et al. 1957, Creamer and Pierce 1957) show a sphincteric function of the lower œsophagus, although no sphincter can be demonstrated anatomically. Why this mechanism should fail when the cardia is situated above the diaphragm could not be explained. Widening of the angle of insertion of the œsophagus into the stomach has been held responsible for regurgitation in hiatus hernia (Franklin 1958, Marchand 1955), but careful radiological measurement of this angle failed to support this view (Atkinson et al. 1958).

Botha (1959) concluded from his extensive study of the cardiac mechanism that the mucosal folds of the cardia acting in harmony with the " internal sphincter " of the lower œsophagus form the closing device between the stomach and œsophagus. The even distribution of pressure along the gastric wall in the normal stomach ensures that there is rarely sufficient localised force to overcome the closing mechanism. In a sliding hiatus hernia the cardia becomes a funnel, directing the intragastric pressure towards the œsophagus. In these circumstances sufficient pressure is more easily built up to give rise to cardiac incompetence.

One of the steps employed by many surgeons in the operation for repair of hiatus hernia is suturing of the fundus to the lower œsophagus. This step was included in the operation in order to re-establish the gastro-œsophageal angle. Although the importance of this angle has been disproved, and Botha (among others) considers this step useless, the impression has been gained that these sutures help to prevent œsophageal regurgitation. In order to test the usefulness of these sutures the following experiments were carried out.

Investigation

4 patients with sliding hiatus hernia who had not responded to conservative treatment were submitted to laparotomy through a left upper paramedian incision.

After freeing of the lower œsophagus, the fundus, and the edges of the œsophageal hiatus, 10 oz. of diluted barium was introduced into the stomach through a stomach-tube. The stomach-tube was withdrawn into the œsophagus. The abdominal wound was approximated and the patient put into the Trendelenburg position. After two minutes an X-ray was taken of the cardiac region, and subsequently the regurgitated barium was aspirated from the œsophagus. After levelling the operating-table, a series of sutures was placed between the left border of the œsophagus and the greater curvature of the stomach, restoring as perfectly as possible the normal anatomical appearances of the cardiac and fundal region. Barium was then reintroduced into the stomach, the stomach-tube again withdrawn, the patient put into the Trendelenburg position, and the wound edges approximated. After two minutes a further X-ray was taken and the amount of barium in the œsophagus again measured.

Fig. 1*a* shows the free gastro-œsophageal reflux in a 52-year-old patient after freeing of the gastro-œsophageal

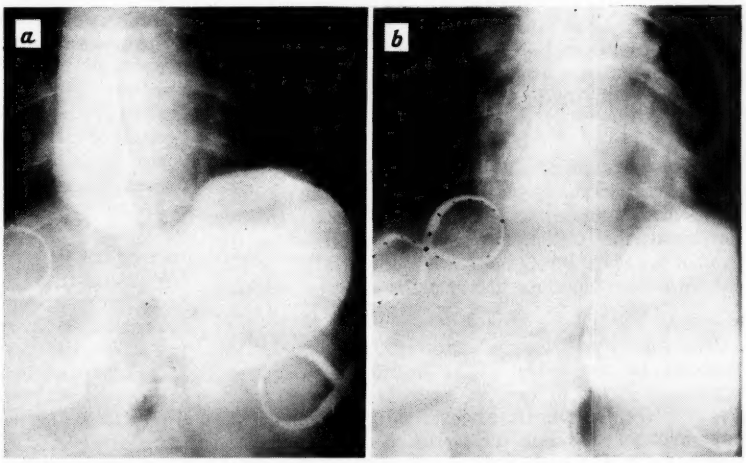

Fig. 1—Case of hiatus hernia in a 52-year-old patient: *a*, gastro-œsophageal regurgitation after freeing gastro-œsophageal region; *b*, absence of regurgitation after stomach was approximated to œsophagus.

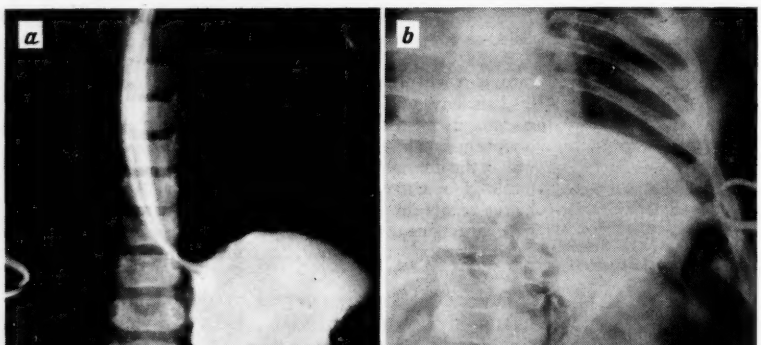

Fig. 2—Case of hiatus hernia in an infant: *a*, free œsophageal regurgitation before insertion of gastro-œsophageal sutures; *b*, appearance after insertion of sutures.

region from the diaphragm. Fig. 1*b* shows the absence of any regurgitation after a fundus was re-created. Fig. 2 shows the same appearances in a baby. Aspiration records show the difference in the amount of reflux before and after the insertion of the gastro-œsophageal stitches (see table).

ASPIRATION RECORDS

Patient's age	Amount introduced (oz.)	First aspiration (oz.)	Second aspiration (ml.)
56 yr.	10	4	0
48 yr.	10	3	4
52 yr.	10	3½	3
9 mos.	4	1	2

The insertion of a series of stitches between the œsophagus and fundus of the stomach was incorporated in 28 operations for repair of a sliding hiatus hernia, and was carried out without repair of the diaphragmatic defect in 2 patients with recurrent hiatus hernia. The operations were performed between 1952 and 1957. The patients included in this series were all operated on through an abdominal approach by a technique similar to that described by Tanner (1958). Of the 28 patients with hiatus hernia, 4 had gallstones also, and were submitted to cholecystectomy at the same time as their herniæ were repaired. 1 patient had a large hydatid cyst above the right lobe of the liver; this was first discovered during laparotomy and had to be removed at a subsequent operation.

Follow-up examination in 1958 showed no residual symptoms from the hiatus hernia in any of the patients. 2 patients had unsatisfactory results. In 1 pyloric stenosis developed (this condition was probably present at the time of the hiatal repair but was unrecognised). The 2nd patient had an incisional hernia of the laparotomy scar.

Discussion

The simple procedure of suturing the fundus of the stomach to the side of the abdominal œsophagus apparently helps to prevent gastro-œsophageal reflux. Prior to the first measurement and radiograph in the experiment, the area of the hiatus was cleared and the hernial sac was excised. Reflux was still free. The fundus was then approximated to the lower œsophagus by two or three sutures. Repeat measurements of œsophageal contents and the second radiograph show that this step alone reduces regurgitation to a very small amount. This conclusion was confirmed in the 2 cases of secondary repair of hiatus hernia, where these sutures alone were employed.

Atkinson et al. (1958) showed that the cardiac angle varied considerably in healthy patients as well as in patients with gastro-œsophageal reflux. It is impossible to recognise the exact site of the gastro-œsophageal junction; and it is difficult to see how an angle, produced even a few centimetres away from the anatomical junction, could re-establish efficient mucosal folds at the cardia. It is therefore not on this angle that the efficiency of these sutures depends.

Botha (1959) has pointed out that the intragastric force is spread over a wider area when the anatomy is normal. It is the fundus which provides most of the area over which any upward pressure is dissipated. It receives most of the gastric contents when intragastric pressure is directed cranially. The thin-walled fundal pouch is then distended and both compresses and angulates the lower œsophagus, which is fixed by the branches of the left gastric artery. This appearance can readily be seen in routine barium-meal examinations. Marchand (1955) showed that the intragastric pressure required to overcome the cardiac barrier when the fundus is clamped off is only a third of that in the intact stomach. In a sliding hiatus hernia the fundus disappears early and the cardiac region resembles a funnel, where any backflow easily enters the œsophagus. In the rolling type of hiatus hernia, a fundus remains and regurgitation does not take place.

Infants regurgitate their feeds with great ease. The diaphragm in infants is an almost flat fibromuscular sheet, allowing little room for fundal development. If the abdominal part of the œsophagus is short, even less fundus can form and free œsophageal regurgitation can take place, leading to œsophagitis in the absence of a hiatus hernia. With growth the diaphragm becomes more arched, with consequent fundal development. Free œsophageal regurgitation will therefore cease and the condition of "lax œsophagus" will not be seen beyond the first few months of life. 4 infants on whom I operated because of œsophagitis due to a "lax œsophagus" were cured by placing a greater length of œsophagus below the diaphragm.

Recurrence after repair of a hiatus hernia has been frequently reported. Wells and Johnson's (1955) recurrence-rate was 30%. In order to prevent the gastric juice reaching the œsophagus additional procedures have been recommended. Tanner usually adds vagotomy to his repair. Wells and Johnson do not repair the hernia but abolish peptic activity by gastrectomy and vagotomy. Merendino and Dillard (1955) used a method of jejunal interposition. Normally a fundus re-establishes itself, even without its being re-formed at operation, when the stomach is placed in its normal position and there is room for a fundus to form. This does not happen invariably, and such variability may be responsible for the uncertain results of the usual repair.

Summary

An experiment was designed to show the reduction in œsophageal reflux after suturing the fundus of the stomach to the lower end of the œsophagus in cases of hiatus hernia.

The presence of a fundus is apparently important in the prevention of reflux.

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THE FREE AMINOACIDS OF PLASMA AND URINE IN KWASHIORKOR

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MUCH information about aminoacid intake can be obtained from a study of the free aminoacids of plasma (Richardson et al. 1953). Such information should be useful in kwashiorkor, which is basically caused by the deficiency of dietary protein; but surprisingly little is known about the free aminoacids of plasma and urine in this syndrome.

Cheung et al. (1955) suggested that there may be an abnormal pattern of excretion of aminoacids in the urine. Hansen, Howe, and Brock (1956) concluded that aminoacids are the chief limiting nutrients of the diet on which kwashiorkor develops. Their nitrogen balance studies showed that nitrogen retention was better on a mixture of 18 aminoacids including all the essential aminoacids than on a mixture of the essential aminoacid alone. Westall (1958) in a study of protein malnutrition in Mexican children found that the level of aminoacids in the plasma was reduced and that all the aminoacids were not affected equally. Senecal (1958) did not find paper chromatography of much value in the study of serum and urine aminoacids in cases of kwashiorkor. Schendel et al. (1959) observed increased aminoaciduria in infants with kwashiorkor.

Here we report on the paper chromatography of the free aminoacids of plasma and urine in 50 untreated cases.

The Investigation

The studies were made on 50 new untreated cases of kwashiorkor in children aged 1–4 years seen in the pædiatric clinic of University College Hospital, Ibadan, in the year ended March, 1959. On admission the children were kept on glucose-water with added potassium until next morning, when fasting blood and urine specimens were collected.

10 ml. of the blood was heparinised and used for aminoacid studies. The rest was allowed to clot and the serum was used for estimating serum proteins (total and paper electrophoresis) and for liver-function tests (thymol turbidity and flocculation, bilirubin, alkaline phosphatase, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase and isocitric-acid dehydrogenase).

After this initial collection, 41 of the patients were treated with a high-protein milk diet, either as outpatients or inpatients (8 were reinvestigated after discharge). The other 9 were treated by two different regimes. The children chosen for this part of the study were not seriously ill and so in no immediate danger. 3 of them were fed for four days on a diet high in carbohydrate but low in protein (glucose-water, corn-meal gruel, garri, and vegetable soup; calculated to contain less than 5 g. protein per day); at the end of this period further samples were collected and the children then received a high-protein diet. The remaining 6 patients were fed for four days on the same basic high-carbohydrate diet with a supplement of 2·0 g. *l*-methionine per twenty-four hours: after collecting further samples these patients were then treated like the others. During their four days on the methionine-supplemented diet 2 of the children had gastro-intestinal hæmorrhage, the cause of which remains unexplained.

The healthy controls were 25 children of the same age range. They belong to a group of 400 who are being studied in order to establish biochemical normals in Nigerian children.

Methods

Total amino-nitrogen.—Folin's method (Varley 1958) was used initially on the plasma but a modification of the ninhydrin procedure (Harding 1916) was employed in the last 15 cases to estimate the amino-nitrogen in the desalted ultrafiltrate.

Paper chromatography.—The equipment and techniques are those described by Smith (1958).

Plasma was deproteinised by ultrafiltration through ultrafiltration shells, and the ultrafiltrate was desalted in an electrolytic desalter. The desalted ultrafiltrate was freeze-dried and the residue finally redissolved in distilled water, so that 0·5 ml. of the desalted ultrafiltrate was taken up in 25 μl. of distilled water. 25 μl. of the

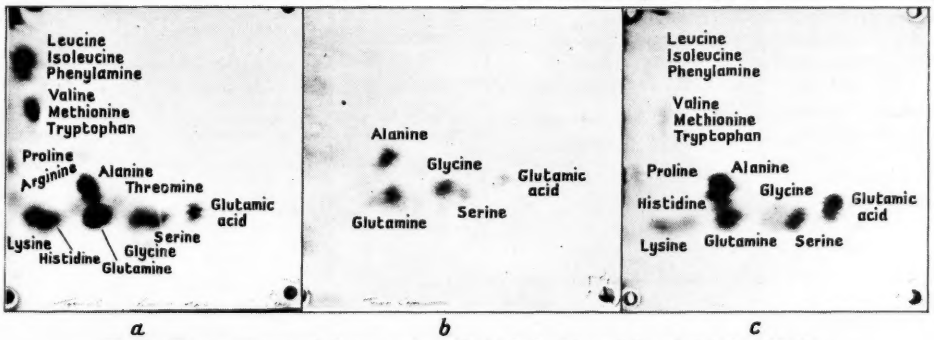
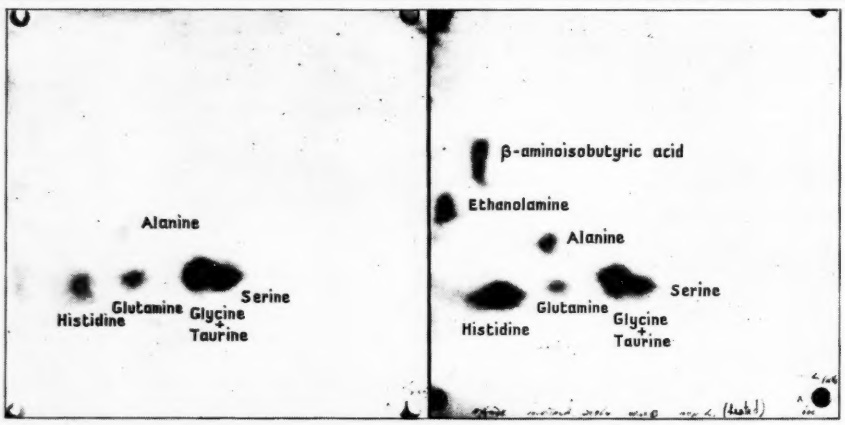


Fig. 1—Chromatograms of plasma aminoacids (*a*) in health, and (*b* and *c*) in kwashiorkor.
Solvents: butanol/acetic-acid/water; phenol/water/ammonia. Colours developed at room temperature.



a *b*

Fig. 2—Chromatograms of urine aminoacids (*a*) in health, (*b*) in kwashiorkor.
Solvents: butanol/acetic-acid-water; phenol/water/ammonia. Papers heated for 2 minutes at 110°C.

concentrated ultrafiltrate was applied to each filterpaper square. The solvent systems used were butanol/pyridine/water or butanol/acetic-acid/water followed by phenol/water/ammonia.

Duplicate sets of papers were usually prepared. The ninhydrin colours in one set were developed at room temperature because this produces better contrast as well as a cleaner background for photographs, which were taken three hours after the papers were dipped in ninhydrin solution. The colours in the duplicate papers were developed by heating for two minutes at 110°C. Besides demonstrating β-aminoisobutyric acid, the heated papers often show substances in low concentration, such as ethanolamine, when they are absent or very faint on the paper developed at room temperature.

50 µl. of desalted urine was applied to each filterpaper square.

Serum bilirubin, thymol turbidity and flocculation, and *alkaline phosphatase* were determined as previously described (Edozien 1958). *Glutamic-oxaloacetic transaminase* and *glutamic-pyruvic transaminase* were measured by the spectrophotometric method (Karmen 1955, Wroblewski and LaDue 1956).

For serum *isocitric-acid dehydrogenase* the method of Wolfson and Williams-Ashman (1957) was chosen but the results have been expressed in spectrophotometric units at 25°C as proposed by Baron (1958, 1959a, b).

Results

Mean values for fasting plasma aminoacid nitrogen in healthy children are 5·2 mg. per 100 ml. (4·1–8·0 mg.) by the method of Folin and 4·3 mg. per 100 ml. (3·5–6·1 mg.) by the ninhydrin procedure. The corresponding mean values in the kwashiorkor patients are 2·5 mg. (2·0–4·5 mg.) and 2·1 mg. (1·3–3·5 mg.). In kwashiorkor, therefore, plasma level of amino-nitrogen is about 45% of normal.

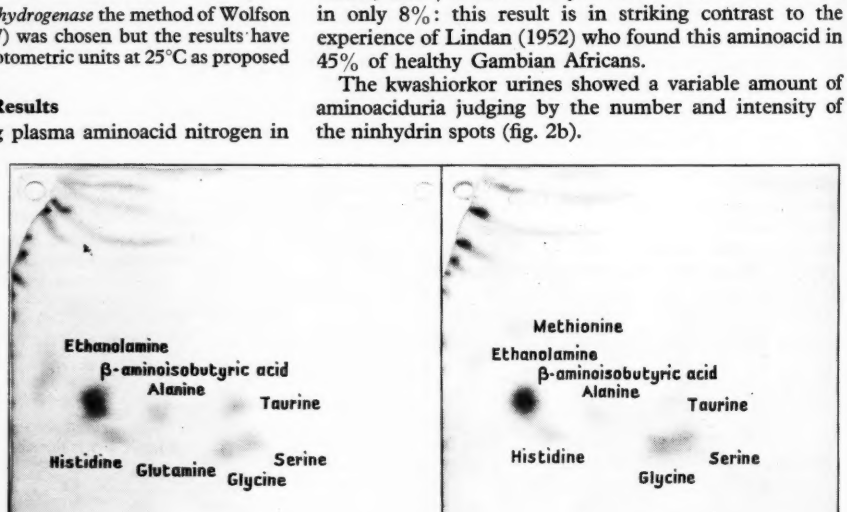
The plasma free-aminoacid pattern in the healthy Nigerian children (fig. 1a) does not differ in any significant respect from that described for European children and adults (Smith 1958). In kwashiorkor the plasma aminoacid chromatograms showed a general decrease in the intensity of the ninhydrin-reacting spots. This loss of intensity, however, is not uniform.

The following aminoacids seem to be most affected (fig. 1b, c): cystine (shown as cysteic acid on samples treated with hydrogen peroxide before being spotted), methionine plus valine plus tryptophan as one spot, leucine plus isoleucine plus phenylalanine as one spot, threonine, and arginine. Because most of these aminoacids are located at the top left-hand corner of the square, in many cases the spots in this region of the chromatogram are hardly visible while the spots in other parts of the chromatogram stand out quite distinctly. It is of considerable interest that all these aminoacids are essential aminoacids. It is also to be noted that lysine did not often behave like the other essential aminoacids.

Ethanolamine could not be detected in any of the normal chromatograms but was clearly visible in about 75% of the cases of kwashiorkor. β-aminoisobutyric acid also could not be located in any of the control plasmas but was found in 30% of the cases of kwashiorkor.

The pattern of aminoacid excretion in the control children was not different in any significant respect from the pattern found in healthy European children (fig. 2a). Ethanolamine was absent from all the control urines, and β-aminoisobutyric acid could be identified in only 8%: this result is in striking contrast to the experience of Lindan (1952) who found this aminoacid in 45% of healthy Gambian Africans.

The kwashiorkor urines showed a variable amount of aminoaciduria judging by the number and intensity of the ninhydrin spots (fig. 2b).



a *b*

Fig. 3—Chromatograms of urine aminoacids in kwashiorkor (*a*) before and (*b*) after 4 days' methionine-supplemented diet.
Solvents: butanol/pyridine/water; phenol/water/ammonia. Papers heated for 2 minutes at 110°C.

TABLE I—EFFECT OF METHIONINE FEEDING ON LIVER-FUNCTION TESTS IN KWASHIORKOR
Group A received control diet, Group B received the methionine supplemented diet

Patient	Total proteins (g. per 100 ml.)	Bilirubin mg. per 100 ml.	Thymol turbidity (Maclagan units)	Thymol flocculation	Alkaline phosphatase (K.A. units)	G.O.T.	G.P.T.	I.C.D.	Plasma ethanolamine	Urine ethanolamine	Urine β amino-isobutyric acid
A.1	4·8 4·4	0·8 0·7	3.5 3·7	− −	16·3 15·8	20·7 16·1	7·7 17·3	5·9 10·7	− −	++ ++	+++ +++
A.2	3·7 3·6	0·2 0·2	2·0 2·3	− −	22·0 23·8	114·0 122·5	70·1 71·0	124·0 118·5	+ +	++ ++	+++ +++
A.3	4·2 3·9	0·7 0·6	5·2 5·7	+ +	14·5 16·3	48·3 49·5	21·7 20·5	12·6 13·8	− −	− −	++ ++
B.1	4·5 4·3	0·7 0·9	4·1 2·9	− −	34·9 23·2	467·5 51·0	110·0 37·6	181·0 21·2	+ −	++ −	+++ ++
B.2	4·3 4·4	1·3 0·6	4·1 2·9	− −	15·3 11·4	15·4 22·4	16·0 16·0	10·0 19·0	+ −	++ −	++ ++
B.3	4·1 4·1	0·8 0·6	0·5 1·0	− −	21·0 16·0	53·6 55·0	27·8 26·6	24·7 24·0	− −	++ +	++ ++
B.4	4·7 4·5	0·6 0·7	0·5 2·4	+ +	14·7 15·4	68·5 52·4	25·0 25·1	15·7 15·7	+ −	+++ +	+++ +++
B.5	3·9 3·7	0·5 0·4	3·1 2·7	− --	16·4 19·0	30·9 30·9	15·3 10·3	17·1 16·6	− −	++ −	++ ++
B.6	4·5 4·2	0·6 0·5	5·8 5·3	+ +	15·8 16·1	51·5 45·4	23·2 21·4	16·5 18·3	− −	− −	+ +

G.O.T. = glutamic-oxaloacetic transaminase. G.P.T. = glutamic-pyruvic transaminase. I.C.D. = isocitric dehydrogenase.

The non-essential aminoacids were chiefly affected: only rarely could essential aminoacids be identified on the chromatograms. Ethanolamine was excreted in 80% of the cases. β-amino-isobutyric acid was identified in every case: indeed in many of the pathological urines it was the dominant aminoacid spot.

The experimental feeding with the high-carbohydrate low-protein diet alone did not noticeably alter the urine chromatograms but there was a distinct reduction in the intensity of the spots in the plasma chromatograms.

The methionine-supplemented diet produced a marked increase in all the plasma aminoacids, including the essential aminoacids. In the 3 cases of this group in which ethanolamine was initially identifiable in the plasma, it disappeared after the administration of methionine. In the urine the excretion of ethanolamine was greatly diminished in all 6 cases (fig. 3): in 3, indeed, it could no longer be identified. The excretion of β-aminoisobutyric acid was unaffected by the methionine (fig. 3). These results are summarised in table I.

Plasma and urine aminoacid chromatograms of the clinically cured patients who were re-examined appeared normal.

Table II gives the mean values for total serum proteins with the protein fractions, and the results of the liver-function tests both in the cases of kwashiorkor and in the controls.

Discussion

Our results with paper chromatography confirm Westall's finding that in kwashiorkor the plasma aminoacids are reduced and that individual aminoacids are affected in different degree. In protein malnutrition there is a qualitative as well as a quantitative deficiency of aminoacids.

The interpretation of the urine chromatograms presents considerable difficulties.

In healthy children and adults comparative urine-aminoacid chromatograms can be produced by applying a timed collection of urine (say 2 seconds urine) or by relating the amount of urine applied to nitrogen content (usually an aliquot containing 625 μg. nitrogen), specific gravity, body-weight, or urinary creatinine output. But in making comparisons between kwashiorkor patients and normal children none of these criteria is satisfactory. The pathological urines are of very low nitrogen content: hence, if aliquots containing 625 μg. of nitrogen are applied, the volumes used constitute much higher proportions of the daily output than is the case with normal urines, and the amino-nitrogen content of these amounts of urine is so high that resolution is impossible. Moreover, most of the pathological urines were of very low specific gravity, and calculations of quantities based on specific gravity also result in application of large volumes of urine. Relating the quantity of urine to body-weight is unsatisfactory because of the œdema. Creatinine excretion is very variable in kwashiorkor because of the muscle breakdown and the decrease in muscle mass which are features of the disease. These and related matters are discussed by Schendel et al. (1959).

Since the technique of paper chromatography is at best only semiquantitative, we do not consider that our method justified any elaborate adjustment of volumes, which in any case appear to be of doubtful value. We have therefore employed the same volume (50 μl.) of early-morning urine in the study of our normal and pathological urines. In 12 kwashiorkor cases (24%) the concentration of aminoacids in the urine was too high for good separation to be obtained, and in these the chromatography had to be repeated with smaller urine volumes.

TABLE II—LIVER-FUNCTION TESTS IN HEALTHY CHILDREN AND IN KWASHIORKOR

Test	Healthy children (1–4 years)	Kwashiorkor (1–4 years)
Total serum proteins	6·9 g. per 100 ml.	4·1 g. per 100 ml.
Albumin	3·2 " "	1·3 " "
α_1-globulin	0·3 " "	0·3 " "
α_2-globulin	0·8 " "	0·5 " "
β-globulin	0·9 " "	0·4 " "
γ-globulin	1·7 " "	1·6 " "
Total bilirubin	0·5 (*0·2–0·9*) mg. per 100 ml.	0·8 (*0·2–1·8*) mg. per 100 ml.
Thymol test (% having turbidity > 4 Maclagan units and flocculation > 1+	0	26
Alkaline phosphatase	27·4 (*17–35*) K.A. units	16·7 (*8–36*) K.A. units
Glutamic-oxaloacetic transaminase	21·9 (*14·0–30·1*) units per ml.	70·5 (*13·6–467·5*) units per ml.
Glutamic-pyruvic transaminase	10·6 (*5·4–17·4*) " "	31·5 (*10·6–110·0*) " "
Isocitric-dehydrogenase	11·3 (*3·3–26·1*) " "	28·7 (*5–181·0*) " "

Our results are in agreement with the report of Schendel et al. that there is increased excretion of aminoacids in kwashiokor. We are strengthened in this conclusion by the fact that, had an attempt been made to relate the volumes of pathological urines applied to their specific gravity, nitrogen content, or creatinine content, we should have applied much larger quantities than we did, with consequent increase in the intensity of the aminoacid spots.

The aminoaciduria in kwashiorkor must be of the renal type, since the increased excretion occurs in spite of the level of aminoacids in the plasma being reduced. Although urine analyses rarely show any urine abnormalities and no specific lesions in the kidneys have yet been described, it still is possible that the renal tubule cells are affected by the generalised loss of cell substance, with consequent decrease in cell proteins including cell enzymes. Individual tubular functions depending on enzyme action may therefore suffer. Recently it has been shown, for instance, that there is an acidification defect in kwashiorkor (Smith 1959). The aminoaciduria could be the result of changes in the enzyme mechanisms responsible for the tubular reabsorption of aminoacids from glomerular filtrate.

It has also been suggested that there may exist in the kidneys a homœostatic mechanism for maintaining the balance of aminoacids in plasma. If this is so, the aminoaciduria in kwashiorkor may be an expression of the imbalance of the plasma aminoacids.

β-aminoisobutyric acid was first identified in human urine in 1951 (Crumpler et al. 1951, Fink et al. 1951), and under ordinary conditions its concentration in the urine appears to be genetically controlled (Crumpler et al. 1951, Harries 1953). Its excretion is increased, however, in various pathological conditions (Walshe 1953, Pare and Sandler 1954, Sandler and Pare 1954). Feeding experiments in the rat (Fink et al. 1952) and in man (Awapara and Schullenberger 1957, Gartler 1959) have pointed to thymine as the probable procursor of this aminoacid.

While the high excretion of β-aminoisobutyric acid in kwashiorkor may be partly the result of increased renal clearance, it is out of all proportion to the increased output of the other aminoacids. Moreover, in a significant proportion of cases (30%) a rise in the level of this aminoacid in the plasma was large enough to be identified by our technique. These findings suggest that it is produced in abnormal quantities in kwashiorkor. Such an excess could be derived from cell deoxyribonucleic acid released by the considerable tissue loss in skeletal muscle and other organs. Moreover, the possibility must be borne in mind that, as a result of the decrease in the protein and aminoacid pool, there may be a general increase in the turnover-rate of cells. This could account not only for an increase in the breakdown of deoxyribonucleic acid but also for the rise in serum glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and isocitric-acid dehydrogenase in cases where there is no other evidence of impaired hepatic function.

An alternative explanation, which would account more satisfactorily for the very considerable increase in the excretion of β-aminoisobutyric acid is that the metabolism of this aminoacid is blocked by deficiency of an essential metabolite or disturbance of an enzyme mechanism; but so little is known about the intermediary metabolism of this substance that there is at present no evidence for this hypothesis.

For some years it has been recognised that ethanolamine is excreted, along with other aminoacids, in liver disease (Dent and Walshe 1951, Walshe 1953). We suspected that the ethanolaminuria in kwashiorkor may be a very sensitive indication of nutritional liver damage, but we could find no constant relation between the plasma-ethanolamine and ethanolaminuria on the one hand and the liver-function tests on the other. Thus about 75% of our cases had a raised level of ethanolamine in the plasma, and 80% had ethanolaminuria; but only 35% had serum-bilirubin levels higher than 1·0 mg. per 100 ml., 26% showed abnormal protein flocculation reactions, and only 2% had alkaline-phosphatase levels higher than 35 K.A. units (the upper limit for the control children). The mean values for glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and isocitric dehydrogenase were higher in the kwashiorkor children than in the control group but no correlation could be established between the enzyme levels and the ethanolaminuria.

Table I shows that, except in 1 patient (B.1), administration of methionine did not unequivocally improve liver function, though it always abolished or greatly reduced the ethanolaminuria. We conclude, therefore, that the overproduction and overexcretion of ethanolamine is the result not of liver damage but of a metabolic block in the utilisation of this amine for the synthesis of choline. This block results from a deficiency of methyl donors which in our feeding test was corrected with methionine.

Summary

The free aminoacids of plasma and urine in kwashiorkor have been studied by paper chromatography.

In kwashiorkor the total aminoacid nitrogen of the serum is reduced to approximately 45% of normal value: the individual aminoacids are affected in varying degrees.

There is an aminoaciduria of renal origin.

Excretion of ethanolamine and of β-aminoisobutyric acid is increased. Evidence is given which suggests that the ethanolaminuria is due to a metabolic block in the utilisation of ethanolamine. The excess β-aminoisobutyric acid could be derived from a similar block in its utilisation, or alternatively from deoxyribonucleic acid released by tissue breakdown and from a general increase in cell turnover rate.

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DEFECTS OF WATER REABSORPTION AND OF HYDROGEN-ION EXCRETION BY THE RENAL TUBULES IN HYPERPARATHYROIDISM

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OVER two hundred years ago Cadwalader in Philadelphia described a patient whose bones were soft, in part dissolved, and full of large holes, like a honeycomb. Four years before her death at the age of 40, she had been "seized with a Diabetes, and the usual symptoms, *viz.* a frequent and copious Discharge by Urine, a gradual Wasting of the Body, a Hectic Fever, with a quick, low Pulse, Thirst, great Pains in her Shoulders, Back and Limbs, and Loss of Appetite" (Bevan 1743, Cadwalader 1745).

This was really the first description of hyperparathyroidism, but the clinical features were not clearly recognised until about thirty years ago. Since then many have noted polyuria to be a symptom of the disorder, though it is seldom as prominent as in Cadwalader's patient. When it is, it may lead to a mistaken diagnosis of pituitary diabetes insipidus. The polyuria of hyperparathyroidism does not, however, respond to vasopressin—because the defect is in the renal reabsorption of water and not in the secretion of antidiuretic hormone (Cohen et al. 1957). This defect has been attributed to the hypercalcæmia, since it may be encountered with hypercalcæmia from other causes (Epstein et al. 1958).

There is some evidence that parathyroid hormone itself may directly impair the tubular reabsorption of water (Epstein et al. 1959).

Ellsworth and Nicholson (1935) and Robbins (1937) noted that parathyroid extract injected intravenously in man increased the excretion of water and of sodium. These observations have been confirmed by Nordin (1959). Epstein et al. (1959) recently showed that parathyroid extract injected intravenously in dogs diminished the maximum concentration of solutes in the urine during dehydration and impaired the reabsorption of water during an osmotic diuresis produced with mannitol. Moreover, during the osmotic diuresis the dogs' urine was often hypotonic despite the fact that they were infused with vasopressin at the same time as mannitol.

A defect in the tubular reabsorption of water is unlikely without other defects of tubular function. Indeed, Ellsworth and Nicholson (1935) found that parathyroid extract decreased the excretion of hydrogen ion in their dogs. The excretion of hydrogen ion has not been systematically investigated in hyperparathyroidism in man, but an impaired excretion of hydrogen ion and a systemic acidosis has occasionally been noted with hyperparathyroidism as well as with hypercalcæmia from other causes (Cohen et al. 1957, Fanconi and Rose 1958, Wrong and Davies 1959).

We have studied the tubular functions of water reabsorption and hydrogen-ion excretion in patients with hyperparathyroidism who did not have polyuria.

* Seconded from the Public Health Laboratory Service of the Medical Research Council.

Procedure

Patients

We studied 6 patients with hyperparathyroidism; 4 of them had kidney stones and 2 had not. We also studied 3 patients without hyperparathyroidism: 2 of them had stones. Table I shows the principal clinical findings in the patients with hyperparathyroidism.

Of the 2 patients without stones, one was a man with multiple tumours of the parathyroids and of the islets of Langerhans whose original symptoms were the result of hypoglycæmia. He showed no radiological signs of bone disease. The other was a woman with a solitary osteoclastoma of the lower end of the right femur but no other evidence of bone disease.

All the patients with hyperparathyroidism had their parathyroid adenomas removed. 4 of them were studied a second time about a week after the operation, and 2 of them a third time two months after the operation.

Tubular Reabsorption of Water

Response to dehydration.—The maximum osmolar concentration of the urine (Crawford and Nicosia 1952) was measured after the patient had been deprived of water for between eighteen and twenty-two hours. (In the patient with hyperinsulinism we failed to carry out this test satisfactorily.)

Response to vasopressin during osmotic diuresis.—The reabsorption of water by the renal tubules was measured during an osmotic diuresis produced by infusion of a 25% solution of mannitol.

Although it is customary to carry out this test in patients deprived of water, our patients had enough water to make the urine hypotonic before the infusion, and during the infusion we encouraged them to drink. We thought that hydration might reveal defects in the tubular response to vasopressin which might not be apparent in the presence of dehydration (Miles et al. 1954).

An initial dose of vasopressin ('Pitressin' 100 milli-units) was given intravenously as soon as the urine became hypotonic, and throughout the experiment vasopressin was infused at the rate of 5 milli-units per min. This rate is more than enough to ensure a maximal response. The mannitol infusion was started one hour after the first dose of vasopressin and continued for at least one hour at a rate of about 5–9 ml. per min.; during this period at least three accurately timed collections of urine were made.

Excretion of Hydrogen Ion

The pH_i titratable acidity and ammonia were measured in specimens of urine collected hourly following the

TABLE I—THE PATIENTS

Patient	Sex and age	Presentation	Hyperparathyroidism	Plasma calcium (mg. per 100 ml.)	Plasma phosphorus (mg. per 100 ml.)	Urine calcium (mg. per 24 hr.)	Blood-urea	Creatinine clearance
A	M 67	Sympathectomy	–	9·5	3·4	302	30	..
B	M 42	Renal stone	–	9·8	3·0	239	22	88
C	M 30	,, ,,	–	10·2	2·9	258	..	125
D	F 50	Osteoclastoma	+	11·6	2·6	355	22	80
E	M 32	Islet-cell tumour	+	14·4	2·5	—	30	150
F	F 40	Renal stone	+	11·8–13·3	2·2	190	22	70
G	F 57	,, ,,	+	13·2–14·3	2·8	135	52	47
H	M 63	,, ,,	+	11·2–11·8	2·4	294	28	74
I	F 56	,, ,,	+	10·6–11·7	2·5	170	30	79

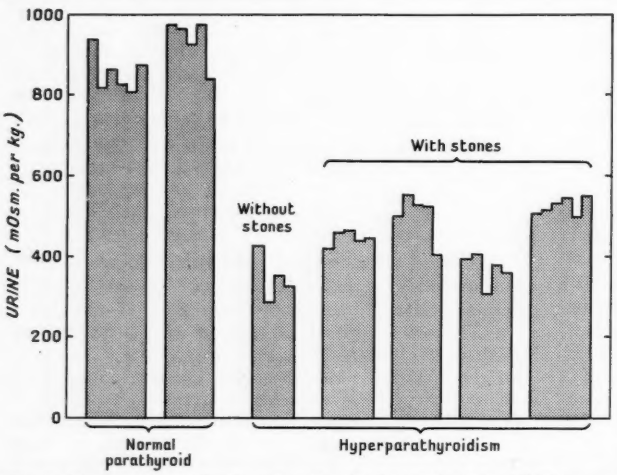

Fig. 1—Concentration of urine after deprivation of fluid for 18–22 hours.

ingestion of ammonium chloride, 0·1 g. per kg. body-weight.

In carrying out this test in 10 people without renal disease Wrong and Davies (1959) found that the pH of hourly collections of urine fell to a mean value of 4·6–5·2 from the second to the eighth hour after the ingestion of ammonium chloride; the titratable acidity rose to a mean value of 24–51 μEq. per min. and the NH_4 to a mean value of 33–75 μEq. per min.

Results

Glomerular Function

Glomerular filtration, measured by the endogenous creatinine clearance, was not much impaired (table I). The lowest value encountered was 47 ml. per min. in patient G; her blood-urea was 52 mg. per 100 ml.

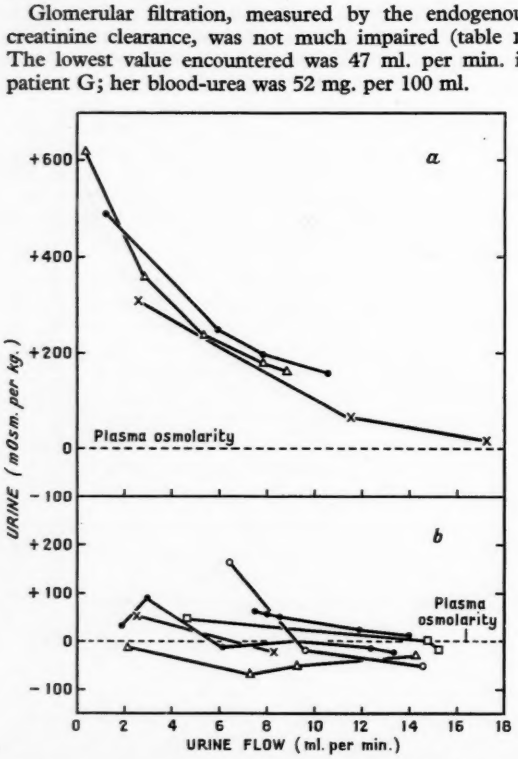

Fig. 2—Concentration of urine at increasing rates of flow during an osmotic diuresis (*a*) in patients without a parathyroid adenoma, (*b*) in patients with a parathyroid adenoma.

Tubular Reabsorption of Water

Fig. 1 shows the effect of water deprivation on the concentration of solutes in the urine. The maximum osmolality of the urine in patients with hyperparathyroidism ranged from 405 to 550 m.Osm. per litre, whereas the normal values certainly exceed 700 m.Osm. and are often greater than 1000 m.Osm. per litre (Miles et al. 1954, West et al. 1955). The normal response to a hypertonic infusion of mannitol with pitressin (Wesson and Anslow 1948, Zak et al. 1954, Barlow and de Wardener 1959) is illustrated by the results in table II, from the 2 patients with stones who did not have hyperparathyroidism. As the rate of excretion of solute increased, the flow of urine increased and its concentration fell; but at all rates of excretion of solute the urine remained more concentrated than the plasma (fig. 2a). By contrast, in 4 of the 6 patients with hyperparathyroidism the urine became more dilute than the plasma (fig. 2b).

The renal tubules concentrate the urine by reabsorbing water in excess of solute. This process takes place in the distal and collecting tubules; under the influence of antidiuretic hormone, fluid which is hypotonic on entering the distal tubules is hypertonic when it leaves the collecting tubules.

As the exact concentration of the hypotonic fluid entering the distal tubules cannot be known, the total volume of water

TABLE II—THE URINE CONCENTRATION AT INCREASING RATES OF FLOW AFTER A HYPERTONIC INFUSION IN TWO PATIENTS WITH RENAL STONES BUT WITHOUT HYPERPARATHYROIDISM

Spec.	Urine flow (ml. per min.)	Urine (mOsm. per l.)	Plasma (mOsm. per l.)	Cosm	T^cH_2O	Creatinine clearance
Patient B						
1 Pitressin given	10·8	70	272	2·75	−8·05	96
2	3·4	151	..	1·77	−1·63	86
3	0·76	636	..	1·61	+0·85	89
4	0·71	797	320	1·81	+0·55	82
Mannitol begins						
5	1·26	808	312	3·28	+2·02	127
6	10·6	473	322	15·75	+5·15	127
Mannitol ends						
7	7·82	517	318	13·27	+5·45	100
8	5·92	500	272	10·78	+4·66	106
Patient C:						
Pitressin given						
1	0·86	765	..	2·16	+1·3	134
2	0·65	1000	305	2·13	+1·48	115
Mannitol begins						
3	0·55	910	..	1·67	+1·12	113
4	2·88	663	285	6·47	+3·59	158
5	5·4	528	..	10·0	+4·6	65
6	7·85	480	285	13·2	+5·35	103
Mannitol ends						
7	8·73	463	..	14·2	+5·47	152

reabsorbed in excess of solute cannot be calculated. One can, however, calculate the amount of water which has to be reabsorbed to bring the tubular fluid from a concentration isotonic with plasma to its final concentration. This amount is denoted by the symbol T^cH_2O (the superscript c standing for "concentrating") and is expressed as "free water"—i.e., water reabsorbed independently of solute.

$$T^cH_2O = \frac{U_{osm} \times V}{P_{osm}} - V$$

where U_{osm} and P_{osm} are the total solute concentrations, in milliosmoles, in the urine and the plasma, and V is the volume of urine per min. The maximum value of T^cH_2O in normal subjects, 5–7 ml. per min., is reached when the urine flow exceeds 7 ml. per min. during an osmotic diuresis (Zak et al.

TABLE III—AMOUNTS OF WATER REABSORBED DURING THE CONCENTRATING PROCESS

Range of values obtained at high rates of flow induced by an osmotic diuresis

Patients without hyperparathyroidism			Patients with hyperparathyroidism		
Patient	T^cH_2O (ml. per min.)	Urine flow (ml. per min.)	Patient	T^cH_2O (ml. per min.)	Urine flow (ml. per min.)
A	+1·4	23	D	+0	14·8
	+2·4	11·2		+0·3	9·0
B	+4·8	7·8	E	−1·1	17·1
	+5·0	10·6		−0·4	8·2
C	+4·6	5·4	F	−0·2	8·0
	+5·5	8·7		+1·8*	12·6
			G	−2·0	7·2
				−1·6*	14·3
			H	−2·4	14·6
				+2·4	20·8

* The collections of urine in these two periods may have been inaccurate.

1954, Berliner et al. 1958, Barlow and de Wardener 1959). If the final urine is hypotonic T^cH_2O is a negative value.

Table III shows the values for T^cH_2O at the height of the mannitol diuresis. The 2 young patients without hyperparathyroidism achieved normal rates of free water reabsorption although they both had renal stones. The 3rd was much older, and this may be the reason for his relatively poor response.

The patients with hyperparathyroidism had abnormally low values; they were negative when the patients were excreting urine hypotonic to their plasma.

Excretion of Hydrogen Ion

After the administration of ammonium chloride, the excretion of hydrogen ion was normal in the patients without hyperparathyroidism, even if they had renal stones; it was also normal in those patients with hyperparathyroidism who did not have stones. In the patients with hyperparathyroidism and stones, however, this function was defective: fig. 3 shows that the average pH of the urine remained about 6 in most cases and never fell below 5·4. The excretion of ammonium was smaller than normal. It bore the normal relation to the pH of the urine (Wrong and Davies 1959). Because the excretion of ammonium was small, the total excretion of hydrogen ion, measured as the sum of the excretion of NH_4^+ and titrable acidity, was less than normal (fig. 4).

In the 4 patients studied one week after their parathyroid adenomas were removed there was little evidence of any improvement. In 2 patients studied again after two months both functions had improved; in another patient they had not improved.

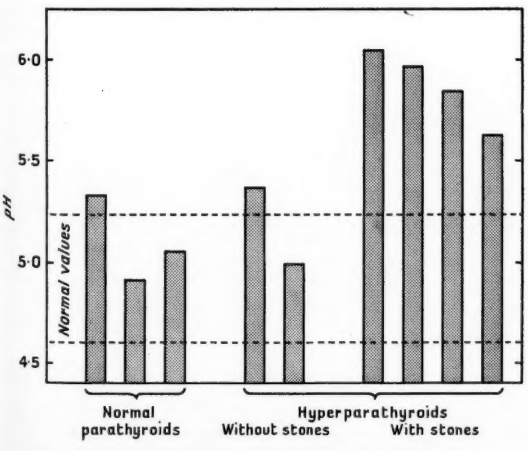

Fig. 3—pH of urine after ingestion of ammonium chloride.

Discussion

It has long been known that one of the commonest and most serious effects of hyperparathyroidism is renal damage leading to uræmia and death. This is the result of renal calcification, stone formation, and infection, and is associated with a severe loss of glomerular function.

Another effect of hyperparathyroidism upon the kidneys is damage to the tubules, which may produce the syndrome of renal diabetes insipidus. When the syndrome is produced in this way it is the result of a high concentration either of calcium or of parathyroid hormone in the body fluids, as is evident from its rapid correction by removal of the abnormal parathyroid tissue (Cohen et al. 1957, Epstein et al. 1958). This syndrome is rare.

Hyperparathyroidism has a third effect upon the kidneys, which is easily overlooked because it does not cause symptoms. Some years ago Hellström (1954) noted that, when they were deprived of water, almost all patients with hyperparathyroidism failed to form urine of normal concentration, although their glomerular filtration-rate and the level of urea in their blood might be quite normal. This suggested that they all had some tubular damage which interfered with their ability to reabsorb water and to produce a concentrated urine (Edwall 1958). Hellström measured the specific gravity of the urine, which gives only a rough idea of the total concentration of solutes.

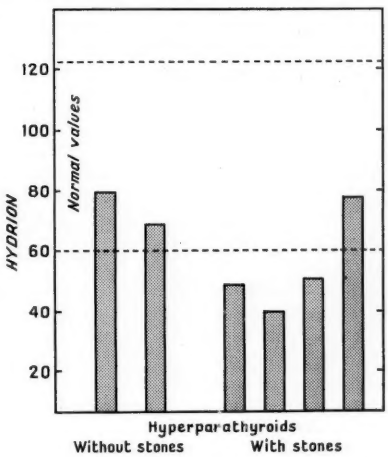

Fig. 4—Excretion of H-ion after ingestion of ammonium chloride.

Measuring the concentration of the urine by its osmolality, we have confirmed Hellström's findings. In addition, we found that, whereas at ordinary rates of solute excretion our patients could produce urine more concentrated than plasma, when they were subjected to an osmotic diuresis the osmolality of their urine fell below that of the plasma although they were having vasopressin. These results show that water reabsorption was depressed. They suggest that, when the rate of flow of fluid through the tubules was increased by an osmotic diuresis, enough water could not be reabsorbed to render isotonic the hypotonic fluid delivered to the distal tubules (de Wardener and del Greco 1955). This abnormality is not generally encountered in renal failure, such as may be produced by nephritis, except perhaps when the glomerular filtration is very much diminished and the volume of the urine represents a large proportion of the glomerular filtrate (Baldwin et al. 1955).

This defect differs in at least two respects from that

previously described in patients with hyperparathyroidism and the syndrome of diabetes insipidus. Firstly, it is much less severe, and the concentration of the urine is not necessarily *below* that of the plasma. Secondly, there is little recovery immediately after operation, whereas patients with the syndrome of renal diabetes insipidus lose their hyposthenuria and are able to produce at least an isotonic urine quite soon after the removal of a parathyroid adenoma.

Persistent hyposthenuria in hyperparathyroidism, with the syndrome of diabetes insipidus, has been attributed to hypercalcæmia. The less obvious disturbance of water reabsorption demonstrated in our patients, however, cannot be the result solely of raised levels of calcium or of parathyroid hormone in the body fluids, since these levels fall a few hours after the removal of a parathyroid adenoma. Morphological changes produced in the kidney by the parathyroid hormone could be responsible for the functional defects. The tubular fluid is concentrated in the distal and collecting tubules, and in hyperparathyroidism calcium is deposited round these segments of the tubules. The deposits of calcium can persist for some time after the removal of a parathyroid adenoma (Cohen et al. 1957, Epstein et al. 1959, Jaccottet 1959).

Hydrogen-ion Excretion and Renal Stone

Impaired reabsorption of water is often associated with a defect in the secretion of hydrogen ion which also takes place in the distal tubule. This is the case, for instance, in the Fanconi syndrome and in the syndrome of renal acidosis (Jackson and Linder 1953, Stanbury 1958). Among our patients this association was found only in those whose hyperparathyroidism was complicated by renal stones. Infection of the urine may have contributed to the abnormal finding; we do not think this is likely but the point is to be investigated further. The patients with stones not due to hyperparathyroidism excreted acid normally. It is therefore interesting to consider the bearing of an inability to acidify the urine upon the formation of renal stones.

In patients *without* hyperparathyroidism stone formation often begins in the pelvis of the kidney with the extrusion of a plaque of calcium from the tip of a renal papilla (Randall 1940). On the other hand, in patients *with* hyperparathyroidism the stone probably originates in the renal tubules as a cast containing calcium phosphate. Although the precipitation of calcium in the renal tubules has naturally been assumed to be the result of a high concentration of calcium in the urine, the finding of more and more patients with hyperparathyroidism and renal stones whose output of calcium in the urine is normal makes this assumption unsatisfactory. In our patients the excretion of calcium was usually not large.

Thus in patient I it was only 60–200 mg. daily; her small excretion of calcium could not be attributed to renal failure, for her creatinine clearance was 79 ml. per min., and her blood-urea 30 mg. per 100 ml. She had bilateral staghorn calculi, and a biopsy of her left kidney, taken when she had a stone removed a month before her operation for a parathyroid adenoma, revealed deposits of calcium around the tubules.

Infection might have played a part in the renal calcification, but one would expect this to lead only to the formation of stones in the pelvis. Since her excretion of calcium was small it may be suggested that the deposition of calcium in the tubules was facilitated by the relatively alkaline reaction of her urine produced by the defect in hydrogen-ion excretion.

We have already suggested that this defect in tubular function might be the result of the initial damage to the tubules produced by the deposition of calcium *around* them, but it is impossible to escape the conclusion that the defect in hydrogen-ion excretion would in turn favour the further deposition of calcium *within* the tubules.

Apart from its theoretical interest, the difference in the ability of these two groups of patients with renal stones to excrete hydrogen ion, would (if confirmed) be of practical value in distinguishing between them. At present a diagnosis of hyperparathyroidism in patients with stones is often largely based on very small changes in the plasma-calcium level; if a simple test of tubular function were to make this diagnosis easier it would represent a great gain. The change in the pH of the urine produced by a dose of ammonium chloride can be measured very easily and the patient does not even have to come into hospital for this to be done. It should not, therefore, be difficult to test the suggestion that, among patients with renal stones, those with hyperparathyroidism fail to excrete hydrogen ion normally.

Summary

The renal tubular functions of water reabsorption and hydrogen-ion excretion were tested in 6 patients with, and 3 patients without, hyperparathyroidism. 4 of the patients with hyperparathyroidism, and 2 of those without, had renal stones.

The reabsorption of water was measured by the osmolality of the urine after water deprivation and by the response to an intravenous infusion of hypertonic mannitol given with vasopressin. These tests demonstrated that the patients with hyperparathyroidism did not reabsorb water normally.

The excretion of hydrogen ion was measured by the changes in pH and excretion of ammonium and titratable acid after the ingestion of ammonium chloride. The 4 patients with hyperparathyroidism and stones did not have a normal fall in the urinary pH; their excretion of ammonium and titratable acid was only slightly diminished. These functions were normal in all the other patients tested. The diminished excretion of hydrogen ion after the ingestion of ammonium chloride in patients with stones due to hyperparathyroidism might therefore have diagnostic value. This suggestion could easily be tested in a clinic devoted to renal stones. Furthermore there is a possibility that a diminished excretion of hydrogen ion with a relatively alkaline urine plays a part in the formation of renal stone in hyperparathyroidism.

The failure to reabsorb water normally, and the impaired excretion of hydrogen ion did not immediately disappear after the removal of a parathyroid adenoma. They are not therefore simply the result of high concentrations of circulating calcium or of parathyroid hormone. They may be the result of a renal deposition of calcium.

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LUNG METASTASES HERALDED BY HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

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SINCE the recognition of hypertrophic pulmonary osteoarthropathy (H.P.O.A.) by von Bamberger (1889) and Marie (1890) independently, many and diverse underlying conditions—involving lungs, pleura, mediastinum, and diaphragm—have been found. In present-day clinical experience, tumours, and notably bronchial carcinomas, cause H.P.O.A. far more often than other well recognised conditions such as pulmonary sepsis.

H.P.O.A. has been described in association with many intrathoracic neoplasms other than bronchial carcinoma. Malignant tumours include fibrosarcoma of the lung (Massachusetts General Hospital case no. 31271 [Mallory et al. 1945]), thymic carcinoma (Miller 1939), and endobronchial plasmacytoma (Plenk and Pretl 1953); benign tumours include localised pleural fibroma (Price Thomas and Drew 1953), neurilemmoma (Trivedi 1958), and neurofibroma (Keller and Callender 1930). Even "pseudotumours" in the thorax, such as aortic aneurysm (Lang and Bower 1930) or gross dilatation of the œsophagus following achalasia or carcinoma (Peyman 1959), seem occasionally to be associated with H.P.O.A. In contrast to the fairly common phenomenon of H.P.O.A. complicating primary intrathoracic neoplasms, its association with hæmatogenous metastases from a non-pulmonary primary source is rare.

We have recently seen a patient who had had a leiomyosarcoma of the uterus removed successfully. 4 years later acute H.P.O.A. developed and was apparently related to "cannon-ball" metastases in the lungs.

Case-report

A woman of 49 was referred to the London Hospital in April, 1954. For several weeks she had had anorexia, morning nausea, feverishness, and a dragging lower abdominal pain, and she had gradually become weaker.

She was well nourished but febrile. Abdominal examination revealed a mass arising from the pelvis and extending towards the left iliac fossa. Her fingers were not clubbed. Before operation she had intermittent fever which did not respond to antibiotics.

At laparotomy (Mr. Victor Lack) the uterus was found to contain two large tumours, and a radical hysterectomy was done. The larger mass was 11 cm. in diameter, with a necrotic centre; histologically it proved to be a leiomyosarcoma, showing numerous giant and atypical cells.

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The patient's sense of well-being rapidly returned, and her temperature became normal on the day after operation. During the next 4 years she was in good health, and even took a reducing diet because of excessive weight gain. In April, 1958, she began to get aching pain over the shins and ankles, particularly towards the end of the day; this slowly increased in intensity and duration. She was readmitted to the London Hospital in July with unremitting pain over the shins and ankles, and to a lesser extent at the wrists.

The patient's state of nutrition had remained good. The most striking abnormalities were clubbing of fingers and toes, œdema of ankles, and warm dusky areas overlying the anterior tibial surfaces. Her shins were so exquisitely tender that she could not tolerate the weight of bedclothes on her legs. Both ankles and wrists were a little swollen and tender. The clubbed fingertips were warm but not tender.

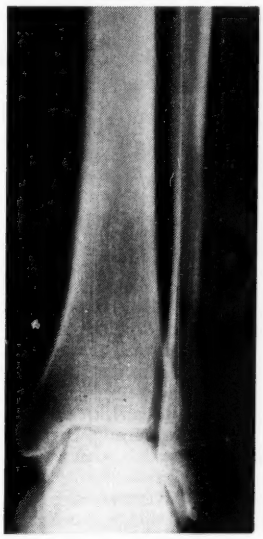

Fig. 1—Subperiosteal bone deposition at lower ends of left tibia and fibula.

H.P.O.A. was diagnosed. This was amply confirmed by the radiological appearance of the shafts of the tibiæ and fibulæ which, in each leg, showed deposition of periosteal new bone (fig. 1). Chest radiographs revealed several discrete rounded opacities in both lung fields consistent with blood-borne pulmonary metastases.

Apart from radiographical evidence of dissemination to the lungs, there was no clear indication of tumour spread to other parts of the body; nor did examination of the pelvis suggest local recurrence of the leiomyosarcoma. Clearly the relief of the bone pain was a pressing need. Calcium aspirin in daily dosage of gr. 100 proved ineffective. Vagotomy was considered but it was not thought justifiable to submit the patient to thoracotomy. Steroids seemed worth a trial, and prednisone was given, 60 mg. daily at first, being reduced after a week to 15 mg. As well as general subjective improvement, the local leg pain lessened impressively within 2 days. When discharged from hospital on Aug. 15 she was able to pursue her normal activities at home. She continued to take prednisone 5 mg. t.d.s.

For many months there was little change in her condition clinically, though serial X-rays showed a gradual increase in the size of the pulmonary deposits (fig. 2), and further periosteal new-bone formation. But by February, 1959, deterioration had become more rapid. Acute pain had returned to the legs and wrists, despite continued treatment with prednisone, and general symptoms, including weakness, anorexia, and weight loss, were prominent. In addition local pain and tenderness over the lower thoracic spine suggested dissemination of the tumour to sites other than the lungs.

In March the patient again entered hospital. She was weak and dyspnœic, with limb and back pain, and a high intermittent fever, accompanied by severe rigors on most days. There was now evidence of further subperiosteal bone formation in the right ulna. Treatment with intravenous nitrogen mustard was ineffective. She died in May, just over a year after the symptoms of H.P.O.A. first appeared.

Postmortem Findings

The body was slightly wasted, with diffuse pale brown pigmentation of the skin, clubbing of the fingers and toes, circumoral hirsuties, and a midline scar from the hysterectomy.

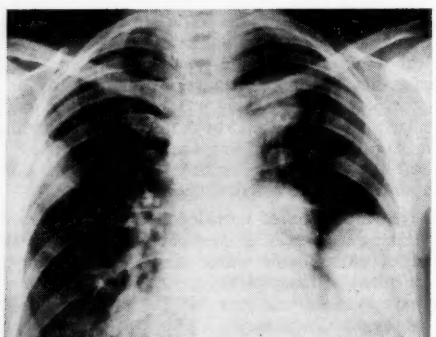

Fig. 2—" Cannon-ball " metastases in lungs.

There was no evidence of local recurrence of the uterine primary sarcoma other than a small nodule overlying the right ovarian vein. Widespread, frequently necrotic, secondary sarcomatous deposits were found in both lungs (the largest measuring 5 × 10 cm.) and invading the adherent parietal pleura over the left anterior basal segment. The visceral pleura, and larger pulmonary arteries and veins, were invaded by sarcomatous nodules from both lungs.

Further sarcomatous deposits were present in one upper left hilar lymph-node, in the intestinal submucosa from stomach to colon, and in the liver, pancreas, right kidney, and suprarenals, although a substantial amount of normal suprarenal tissue remained. Sarcomatous deposits were also found in the D11 and D12 vertebral bodies, and in the right femur.

In addition there was a scar of an old posterior cardiac infarct, bilateral cystic mastitis, hyperostosis frontalis interna, and subperiosteal new-bone formation in the right femur and tibia. The other long bones were not examined.

Histology.—The secondary sarcoma resembled the primary, showing various degrees of differentiation from slightly atypical spindle-cells to multinucleate giant-cell forms, with corresponding variability of myofibrils and reticulin fibres. In several of the pulmonary deposits fine collagen fibrils had coalesced in some areas to form broad bands of mature collagen. These scarred foci were found chiefly near the necrotic areas. The lungs showed widespread and moderately severe stenosis and obliteration of respiratory bronchioles, with early centrilobular emphysema. The anterior lobe of the pituitary (weight 0·8 g.) showed vacuolation but no hyalinisation of the relatively infrequent basophil cells; the acidophil cells were increased.

Discussion

Whatever the exact mechanisms involved in the production of H.P.O.A., they are clearly not primarily dependent upon the type of pulmonary disease, though the prevalence and mode of presentation of H.P.O.A. differs according to the nature of the intrathoracic lesion.

Relevance of Tumour Type

In nearly all collected series, bronchial carcinomas predominate as the tumour underlying H.P.O.A., but this may merely reflect the increase in bronchial carcinoma in recent years; the incidence of H.P.O.A. is in fact small—probably less than 2% (Semple and McCluskie 1955). In contrast, other intrathoracic growths, notably fibrous growths of the pleura, are associated with H.P.O.A. relatively more often.

In six cases of fibroma of the visceral pleura described by Price Thomas and Drew (1953) no less than four presented with joint symptoms. Polley et al. (1952) reported twenty-four cases of localised fibrous mesothelioma of the pleura of whom eighteen had articular symptoms, ten with the full changes of H.P.O.A.

Fibrosarcomatous metastases are more likely to cause H.P.O.A. than any other tumour which disseminates to the lungs. But H.P.O.A. is rarely associated with hæmatogenous spread from a non-pulmonary source, though Mendlowitz (1942) points to the preponderance of sarcomatous deposits, particularly when derived from primaries in bone. Metastatic sarcomas, though relatively less common, are much more often associated with H.P.O.A. than are metastatic carcinomas.

Apart from secondary sarcomas, few secondary lung tumours have caused H.P.O.A. Isolated examples of H.P.O.A. have been seen in cases of pulmonary spread from primaries in breast, adrenal, and possibly parotid (cited by by Mendlowitz 1942).

Relevance of Anatomical Site and Rate of Tumour Growth

It has been suggested that the anatomical situation of the tumour within the lung is important, peripheral lesions being more prone to cause H.P.O.A. In addition, of course, the rate of growth must be slow enough to allow the bone changes to take place. The histological characteristics of the tumours most likely to cause H.P.O.A. are not necessarily their most important feature.

Treatment

Inevitably the approach to treatment must be empirical so long as the exact mechanism by which pulmonary lesions initiate H.P.O.A. remains obscure. But it is of interest that after removal of a primary bronchial carcinoma in some patients with H.P.O.A. bone changes have disappeared, and, later, lung secondary deposits have arisen without return of H.P.O.A. No clear explanation can be offered for these observations, but it seems unreasonable to postulate that a primary bronchial carcinoma has inherently different properties from its seedlings.

Steroids may be used palliatively when operative removal of the thoracic growth, or vagotomy, are impracticable, as in our patient.

de Sèze et al. (1952) described the case of a man of 57 with severe pain in the limbs due to H.P.O.A., who had a rounded opacity in the left chest. He refused operation, and was treated with cortisone. The pain disappeared within 5 days, only to return when the steroid was withheld. Hammarsten and O'Leary (1957) reported significant relief of bone pain when cortisone was given to six patients with H.P.O.A.

Semple and McCluskie (1955) emphasise that in H.P.O.A. remission of joint symptoms may be spontaneous or may apparently follow radiotherapy to the lung tumour; in addition pain may disappear after the use of nitrogen mustard, corticotrophin, or gold. Some of these forms of treatment are directed at the thoracic lesion, and others may act peripherally on the bones and joints. Flavell's experience (1956) that vagotomy gives dramatic relief of bone pain suggests a neurogenic link in the causative chain.

Summary

A woman presented with symptoms of hypertrophic pulmonary osteoarthropathy (H.P.O.A.), and was found to have pulmonary metastases, 4 years after the removal of a uterine leiomyosarcoma.

Tumour type is important in determining whether H.P.O.A. develops. Although sarcomas are rare, H.P.O.A. is much more often associated with their pulmonary metastases than it is with carcinomatous metastases.

Steroid therapy temporarily relieved her bone pain without affecting the progress of H.P.O.A.

Rate of growth and situation in the lung may be the most important features of tumours in initiating H.P.O.A.

We should like to thank Mr. Victor Lack and Dr. N. L. Rusby, under whose care the patient was admitted, for their help with this paper, and for permission to publish.

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PROGRESSIVE LENTICULAR DEGENERATION WITHOUT LIVER DAMAGE IN A YOUNG CHILD

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REVIEWING the modern biochemical predication of hepatolenticular degeneration, Warnock and Neill (1958) pointed out that the original syndrome, so clearly described by Wilson in 1912, has " become clouded by the progress of events ", and that in recent years more and more weight has been given to underlying biochemical anomalies as absolute criteria of the condition. They conclude, however, that " laboratory evidence is seldom, if ever, definite enough to confirm the diagnosis, in isolated cases, without the presence of Kayser-Fleischer rings ". The position is made even more difficult by reports of cases which show the cerebral morphological changes of Wilson's disease unaccompanied by structural liver disease. This has led Brzezicki (1937) to use the term " cerebral Wilson's disease ", and is yet another indication of the difficulties which accrue from insisting on rigid " pigeon-holing " of diseases on the basis of an original and striking description.

Wilson's disease has become more clearly defined as a condition essentially associated with disordered copper metabolism and increased copper storage in the brain and other tissues (see Cumings 1959). But puzzling cases occur from time to time, and " it is important that cases . . . which do not conform to the modern chemical criteria of Wilson's disease should be fully recorded " (Greenfield 1954). The following case, which presented a considerable diagnostic problem during life, is certainly not one of Wilson's disease as at present defined biochemically, but we thought the unusual transitional features should be recorded.

Case-report

CLINICAL HISTORY

The patient, a girl, was an only child born of healthy parents, when they were 28 and 26. The family history was irrelevant, and the mother had had no previous pregnancies.

Fœtal and Newborn Period

Apart from troublesome vomiting, pregnancy was considered normal. The fœtus presented as a breech; external version, attempted at 37 weeks, was unsuccessful, and the infant was delivered as a breech in hospital 5 days before the expected date. Labour lasted 12 hours; towards the end the fœtus was distressed, and for a short time before delivery the fœtal heart was not heard. Birthweight was 7 lb. The mother was told that the infant had had a " rough time ". Because of this the baby was kept in the nursery for the first 3 days; thereafter she was breast-fed for 6 weeks. She seemed well during this time, and neither sucking nor swallowing was difficult.

Later Development

The child sat up, with a straight back, at 7 months. She pulled herself on to her feet and began to walk with support at 14 months. Development was then delayed by whooping-cough, and not until 18 months did she walk unaided. She pronounced single words at 15 months, and phrases at 2 years; speech was intelligible from the beginning. She had measles at 4 years 10 months. She never had an illness associated with excessive drowsiness or delirium.

Development of the Illness

The parents had noticed from birth that the child had always been content to remain still. She was never as adventurous as other children, and she did not play with them, because her legs were so clumsy—" as though she had two left feet ". Because of this clumsiness, which did not improve as she grew older, specialist advice was sought at the children's department of the Royal Victoria Infirmary, Newcastle upon Tyne, when she was *6 years* old. The clumsiness was evident when she ran, but no abnormal neurological signs were elicited.

The clumsiness quickly became more striking, and she fell so often, that whilst on holiday at the age of *6 years 3 months* she was admitted to the Royal Aberdeen Hospital for Sick Children under the care of Prof. John Craig for investigation. Her gait was ataxic, and she stamped on the ball of her left foot as she walked. The left hand and leg were slightly ataxic on formal testing. There was no papillœdema; but, as a cerebral tumour was considered possible, ventriculography was performed by Mr. W. M. Nichols. This showed no ventricular dilatation or displacement. " Cerebellar degeneration " was diagnosed tentatively.

When aged *6 years 8 months* the girl was seen at the Royal Victoria Infirmary by Prof. Donald Court. She was unable to run or walk normally, and she could not hop, skip, or jump; she undressed slowly, having great difficulty with buttons and bows. Her tendon reflexes were brisk, with bilateral unsustained ankle-clonus, and the plantar responses were equivocal. She was thought at this time to have a mild ataxic form of cerebral palsy. To our surprise, during the next year the child's symptoms steadily increased and the ataxia became worse in her right leg. She was seen again at the age of *7 years 11 months* by Professor Court and Dr. Henry Miller. Walking was very difficult and slow, and she now turned her right foot inwards. In the arms muscle-tone was variable, and occasional involuntary movements were seen. All tendon reflexes were brisk; the right plantar response was extensor and the left was equivocal. The diagnosis of torsion spasm was considered, but the involuntary movements and the recent deformities of posture were attributed to the late onset of choreoathetosis. Aminoaciduria was now well marked; most aminoacids were present, including cystine. The serum-copper was 104 μg. per 100 ml.

By the age of *8 years 2 months* the child could not move individual fingers, and power was diminished in both hands. She could make all speech sounds normally in isolation, but some slurring and weakness of consonants appeared when she

tried to speak quickly or when she was tired. There was some weakness of the lips and palate. At *8 years 4 months* she was given primidone 45 mg. t.d.s.; as a result, it seemed, her voice became stronger and her walking steadier. Boots, a short leg calliper, and an outside T-strap were ordered to correct the position of her right foot.

In view of the steady progression of symptoms and the baffling nature of the illness, arrangements were made for the child to be admitted to the National Hospital, Queen Square, under the care of Dr. Arnold Carmichael. Meanwhile she had a number of violent headaches (2 or 3 a day) which frightened her and made her cry out, but which lasted only a few minutes.

While in the National Hospital (aged *8 years 9 months*) she had three seizures in which her head jerked to the right. Her eyes also turned to the right, and the right angle of her mouth twitched. Her right arm made clonic movements, but consciousness was not lost. An air-encephalogram was within normal limits. Electroencephalography showed a significantly fast rhythm in the left temporal region, but no evidence of a localised lesion. Dr. Carmichael agreed that the signs were those of cortico-spinal degeneration of unknown ætiology. The patient was discharged from hospital, taking primidone 250 mg. t.d.s., which controlled her seizures completely.

At *8 years 11 months* there was a rapid deterioration. Ataxia and weakness increased; tremor, drowsiness, and a right lower-motor-neurone facial weakness, with deviation of her tongue to the right, developed. The child was admitted to the children's

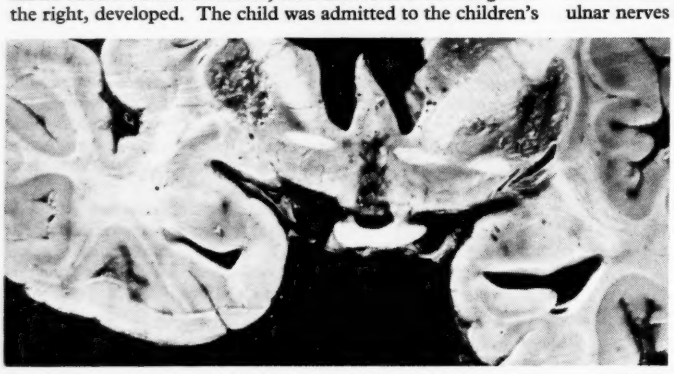

Fig. 1—Coronal section at level of optic chiasma showing bilateral cavitation of lentiform nucleus.

department of the Royal Victoria Infirmary, where primidone was thought to have caused her rapid deterioration. When this drug was discontinued she improved rapidly, and her cranial nerve palsies disappeared almost completely. Variable hypotonia was again found, but no torsion spasms were seen. She was given phenobarbitone gr. $^1/_2$ b.d. and sodium phenytoin gr. $^3/_4$ b.d.

On returning home she was unable to walk unaided, but she seemed happy to sit, lacking the inclination to do anything. Her speech became so weak that at times it was barely audible. Often it was unintelligible. By the age of *9 years 2 months* walking was impossible. She had difficulty in swallowing, first solids and then fluids. She had frequent seizures which could not be controlled by anticonvulsant therapy. 48 hours before death she vomited repeatedly, and during the last 24 hours she seemed to have severe spasms of abdominal pain. She died at the age of *9 years 3 months*.

POSTMORTEM FINDINGS

Necropsy was performed 6 hours after death. The height was normal (4 ft. 2 in.), but the body weighed only 13 kg. (average 26 kg.). There was a growth of very fine hair over the entire body but no other external abnormalities. The hands were fixed in a curious " athetoid " position.

The tongue, pharynx, and œsophagus showed no significant abnormalities. The stomach contained some " coffee-ground " material without evidence of ulceration or other source of bleeding.

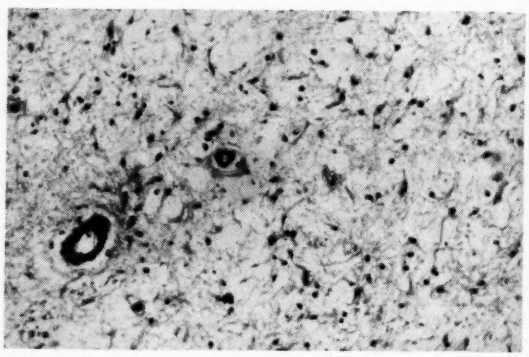

Fig. 2—Left putamen showing open meshwork of astroglial cells with disappearance of nerve-cells. (Hæmatoxylin & eosin. ×129.)

The liver weighed 500 g. (average 736 g.) and was pale chocolate-brown. Section showed no macroscopic evidence of cirrhosis, and this has been confirmed histologically. All other viscera were normal.

The brain weighed 1300 g. (average 1273 g.) and showed no external abnormality. The spinal cord and the femoral and ulnar nerves all appeared normal.

Nervous System

On sectioning the brain, softening with cavitation was found in the putamen on both sides, extending forward into the head of the caudate nucleus and to some extent medially into the globus pallidus, especially on the right (fig. 1). Because the head and body of the caudate nucleus was small, the lateral ventricle, especially in its anterior horn, was a little enlarged, and small ependymal granulations were visible. No naked-eye changes were seen in sections of the brain-stem or spinal cord.

Blocks of tissue were taken from the region of macroscopic degeneration on both sides to include caudate and lentiform nuclei, thalamus, and subthalamus; from the frontal, motor, and occipito-parietal cortex of both sides as well as Ammon's horn; and from the mid-brain, medulla (at midway level), and spinal cord (at C5, mid-thoracic, and L1 levels). The tissues were embedded in paraffin and stained with hæmatoxylin and eosin, van Gieson's stain, phosphotungstic acid hæmatoxylin, and by Loyez and Holzer's method. We had considerable difficulty in obtaining adequate frozen sections through the gross lesion in the putamina, but its margins were examined after being stained with Scharlach R and hæmatoxylin.

Microscopical examination showed that lesions were more widespread than appeared to the naked eye, but of the same general nature. There were more in the putamen than anywhere else. Nerve-cells, both large and small, were much

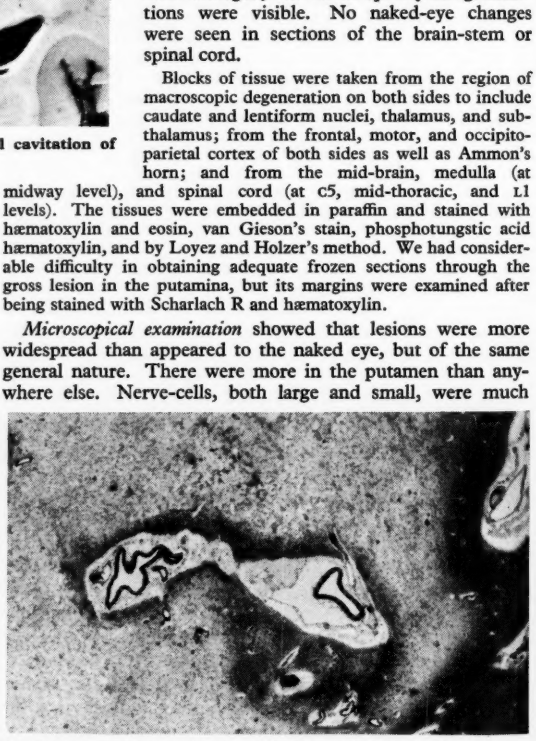

Fig. 3—Left putamen showing dilatation of perivascular spaces. (H. & E. ×13.)

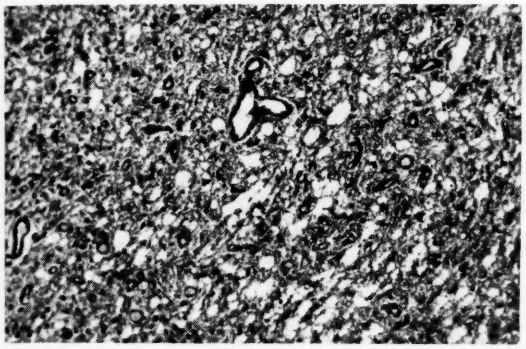

Fig. 4—Subthalamic nucleus showing spongy state, prominent capillaries, and paucity of nerve-cells. (H. & E. ×81.)

reduced in number, and those remaining were almost devoid of Nissl substance. The whole putamen stood out clearly on low-power examination because it was pale and transparent, having been replaced by a loose spongework of glial tissue in which capillaries were numerous and prominent. There was no dense gliosis; the glial open meshwork was loose and had presumably contained gelatinous fluid (fig. 2). Gliosis was well defined around many blood-vessels. Despite careful search no Alzheimer glial cells were recognised, though one or two astroglial nuclei were larger than normal. No Opalski cells were seen. A striking feature was the great dilatation of perivascular spaces around the vessels in the putamen (fig. 3). No myelinated fibres remained in the putamen, but the globus pallidus was relatively little disturbed. Copper could not be demonstrated histochemically in these lesions.

COPPER ESTIMATIONS

Tissue	Copper content (mg. copper per 100 g. dry brain)	Water content (%)
Cerebral white matter	4·03	69·6
Cerebral cortex	3·34	84·5
Basal ganglia	2·09	74·5
Cerebellar white matter	2·95	69·6
Cerebellar cortex	1·58	83·6

The above changes extended slightly into the outer part of the globus pallidus especially on the right, but did not affect the claustrum. A few compound granular corpuscles infiltrated the adjacent fibres of the pyramidal tract which themselves appeared intact. The amygdaloid nucleus and cornu ammonis were not affected on either side. Similar changes of slightly lesser degree were found in the subthalamic nucleus of Luys (fig. 4) and in the substantia nigra. Small scattered areas in the cerebral cortex, especially the parietal and temporal regions, also showed minor changes; these were mainly in the more superficial layers of the cortex and were not noticeable to the naked eye (fig. 5).

Fig. 5—Cerebral cortex from left parietal region showing irregular pale area in the superficial layers. (H. & E. ×3·5.)

They formed isolated islands, and had much the same microscopic appearance as the main lesion in the putamen.

The white matter was unaltered. Occasional brightly sudanophilic compound granular corpuscles were clustered round small subcortical vessels, but these were few and scattered. Holzer preparations showed a moderate degree of subependymal gliosis in the lateral ventricles.

In the medulla oblongata the perivascular spaces were dilated. The interior of the olive on both sides was spongy; many cells showed chromatolysis and vacuolation of their cytoplasm, and occasional enlarged naked astroglial nuclei, which resembled Alzheimer type-II cells, were found.

The cerebellum was normal. In the spinal cord only an occasional anterior-horn cell showed chromatolysis.

Copper content.—Prof. J. N. Cumings of the National Hospital, Queen Square, carried out copper estimations on various parts of the brain. His results (see table) fall within the normal range, excluding the diagnosis of Wilson's disease as it has come to be defined biochemically.

Discussion

The gross and microscopic lesions in the nervous system of this patient resemble those found in the brain in true (biochemically defined) Wilson's disease. The term "hepatolenticular degeneration is more misleading than informative for it leads many to believe that the changes in the brain are limited to the lenticular nuclei" (Lichtenstein and Gore 1955). Neither Alzheimer nor Opalski cells were found in the present case, and their absence suggests that liver function had not been long deranged.

Brown (1957) has found that Alzheimer cells are by no means pathognomonic of Wilson's disease, being seen in many different conditions and in brains of patients without liver disease. He claims to have found them in considerable numbers in erythroblastosis fœtalis (premature), paralysis agitans, Huntington's chorea, tuberose sclerosis, Alpers' disease, Marie's cerebellar ataxia, multiple sclerosis, Krabbe's disease, cerebral arteriosclerosis, cerebral contusion, the border zone of glioblastoma multiforme, and in two normal brains. He therefore suggests that though Alzheimer cells are more numerous when hepatic disease is present, they should not be regarded as characteristic.

It is difficult to know what significance should be attributed to the aminoaciduria found at the single examination of the urine made during life. Dr. A. J. Smith reported as follows:

Partition paper chromatography on the patient's urine, on May 13, 1957 (i.e., 15 months before her death), showed a well-marked aminoaciduria. The pattern was similar to that found in acute liver disease.

Urine from each of the patient's parents was examined on two occasions after her death. The first time both appeared chromatographically to have aminoacids at the upper border of normal, although their urinary aminonitrogen content was normal. But when the investigations were repeated both urines were normal.

The main interest of this case lies in the changes in the brain, which are similar to those found in Wilson's disease (but without Alzheimer or Opalski cells). There was no structural liver damage. Copper metabolism was not disordered. Like that reported by Greenfield (1954), this case has anomalous features which do not readily fit into any scheme of classification.

Greenfield's patient was a woman of 41 who presented an "unusual combination of Parkinsonism and intention tremor sometimes seen in hepatolenticular degeneration but rare otherwise". There was no Kayser-Fleischer ring and no aminoaciduria. At necropsy the liver was found to be cirrhotic. The caudate nucleus

and putamen were shrunken. Alzheimer glial cells were common. There was no abnormal copper storage in brain or liver. Greenfield concluded that this case " may be classed as hepatolenticular degeneration, although it was atypical in several respects, but chemically it was entirely different. . . . Cases like this are probably not very rare, but as the biochemical changes of Wilson's disease are recent discoveries they have not yet been reported. Their classification raises a difficult problem, since the biochemists exclude them from the category of Wilson's disease. . . . Meanwhile it is important that cases such as this, which do not conform to the modern chemical criteria of Wilson's disease, should be fully recorded ".

The position is further complicated by reported cases of " Wilson's disease " without liver involvement. All of these, reviewed by Eicke (1957), date from before the period of biochemical definition of Wilson's disease; hence one cannot be sure that they are indeed that condition. Only the accumulation of further cases which are biochemically documented can clarify the issue. Our case serves to underline the question raised by Greenfield (1954)—" Is hepatolenticular degeneration a clinico-pathological entity? "

Summary

A girl, who died at the age of 9 years 3 months, had the morphological changes of " Wilson's disease " in the central nervous system without hepatic cirrhosis. Copper metabolism was not disturbed but aminoaciduria was present. She had no Kayser-Fleischer ring.

This case cannot be grouped with Wilson's disease as biochemically defined at present.

Our thanks are due to Prof. Donald Court for permission to publish this case; to Prof. J. N. Cumings for the copper estimations and for permission to publish table I; to Dr. A. J. Smith for the urine chromatography; and to Mr. C. J. Duncan of the department of photography for fig. 5.

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FAVISM IN A CYPRIOT CHILD

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FAVISM is a form of acute hæmolytic anæmia which occurs in certain sensitive subjects after eating broad beans. Most cases are said to arise in persons of Sardinian ancestry (Luisada 1941), but the disease is quite widespread throughout the Mediterranean seaboard and islands (Marcolongo 1953) and has been recognised in Hebrew children (Robinson 1941). Owing to this racial predisposition favism is rarely seen in this country. Two cases in Cypriot children in London were described by Diggle (1953) and another was recognised by Discombe and Mestitz (1956). At least one case has been seen in an English child, whose maternal uncle may have suffered from the disease (McCarthy 1955).

Favism is a serious disease, especially in children, in whom the mortality-rate may reach 8% or 10% (Luisada 1941, Marcolongo 1953). Renal impairment and lesions of the basal ganglia are occasional sequelæ (Marcolongo 1953). For these reasons, and because favism is preventable, we have recorded the following case, which also serves as a reminder that Cypriot children may suffer from red-cell defects other than the hæmoglobinopathies.

Case-report

First Admission

A three-year-old boy, the second child of healthy Cypriot parents, was admitted to Edgware General Hospital on July 11, 1958, with a history of rapidly increasing pallor and the passage of dark-red urine for twenty-four hours. The child had complained of pain in the neck and had vomited several times. He had previously been fit except for recurrent sore throat. There was no history of any familial disease.

On examination the child was restless and obviously ill. He was very pale and slightly jaundiced. The temperature was 100°F; pulse-rate 132, and respiration-rate 28 per min. The tonsils were enlarged and injected. A few small glands were palpable in the neck and left axilla. The spleen and liver were not felt and there were no other physical findings of note. A clinical diagnosis of acute hæmolytic anæmia, possibly due to streptococcal throat infection, was made.

Investigations.—Hæmoglobin 3·6 g. per 100 ml. (26%). White cells 15,300 per c.mm. Blood-film showed many fragmenting cells and occasional microspherocytes. A few myelocytes and normoblasts were present. Platelets were plentiful. Direct Coombs test negative, using Coombs serum at dilutions 1/5, 1/20, 1/80. Blood-urea 75 mg. per 100 ml. Serum-bilirubin 4 mg. per 100 ml. The urine was almost black in colour and the deposit contained a few red cells and granular casts. Spectroscopy showed the presence of oxyhæmoglobin and methæmoglobin. Three throat swabs were taken in the first two days but none yielded *Streptococcus pyogenes* or other pathogenic bacteria on culture.

Course and Treatment

The provisional diagnosis was revised to acute exacerbation of a congenital hæmolytic anæmia, but in view of the clear need for urgent blood-transfusion we decided to defer more extensive investigation until the patient was in remission. Two bottles of compatible packed cells were transfused on the same day. No difficulty was experienced with the cross-matching or transfusion of the blood. Although the Coombs test was negative 25 mg. of cortisone was given intramuscularly, followed by 5 mg. of prednisolone daily for six days. In view of the apparent tonsillitis a course of penicillin was also given. The hæmoglobin level on the day following transfusion was 9·9 g. per 100 ml. and did not subsequently fall below this level. Clinical improvement was rapid, hæmoglobinuria ceasing during the second day in hospital. The blood-urea and serum-bilirubin levels fell to normal by the third day. The spleen became palpable on the third day but had disappeared beyond the costal margin two days later. The patient was discharged home on the eleventh day, looking very well, with a hæmoglobin level of 10·8 g. per 100 ml. and a reticulocyte-count of only 1%. One month later his blood-picture was quite normal.

The child was seen again three months later. He was fit and lively, and no abnormality was found on physical examination.

Investigations.—Hæmoglobin 12·4 g. per 100 ml. (87%). Reticulocytes less than 1%. The stained film showed no morphological abnormality of the red cells; in particular no spherocytes, target cells or macrocytes were seen. The leucocytes and platelets were normal. The osmotic fragility of the red cells was normal and incubation autohæmolysis (Selwyn and Dacie 1954) was less than 1% even without glucose. With glucose added there was no detectable hæmolysis after forty-eight hours. Acid hæmolysis test negative. Red-cell potassium 82 mEq. per litre. Electrophoresis showed no abnormal hæmoglobin.

We concluded that the child was unlikely to be suffering from even a mild congenital hæmolytic anæmia.

The patient was seen again in January, 1959, as he had been unwell for a few days. No abnormality was found on examination, but his hæmoglobin level was only 9·0 g. per 100 ml.

Second Admission

He was readmitted to hospital on March 13, 1959. He had developed a sore throat several days previously and for twenty-four hours he had been passing dark-red urine. Examination revealed no physical abnormality and the child was not nearly so ill as on his first admission. Direct inquiry revealed that he had eaten broad beans, which had been purchased frozen, on the day before the onset of hæmoglobinuria. We then discovered that this little boy did not like broad beans and had eaten them only twice before. The first time was just before his serious episode of hæmolysis and the second time was a few days before he was seen in January, 1959, and found to be a little anæmic. The diagnosis of favism was apparent. The child made a rapid recovery without transfusion.

Investigation on this occasion again failed to reveal any evidence of red-cell defect, but at a later date when the patient had a normal blood-picture (hæmoglobin 12·0 per 100 ml., reticulocytes 1·4%), we were able to show that his red cells behaved abnormally after incubation with acetylphenylhydrazine, using the method described by Beutler et al. (1955), for the detection of " primaquine-sensitive " red cells. This test was unequivocally positive, 80% of the patient's erythrocytes developing multiple small Heinz bodies, compared with 27% of the normal control.

Discussion

Until recently favism was regarded as an " allergic " response to the proteins of broad beans, but Larizza et al. (1958) have demonstrated an intrinsic red-cell defect in patients with favism, both during the active phase of the disease and after recovery. This defect is identical with, or at least closely related to, the intrinsic abnormality found in patients in whom hæmolysis develops in response to primaquine, sulphonamides, and nitrofurantoin (" primaquine sensitivity " or " primaquine anæmia "). Beutler (1959) and others have shown that the erythrocytes of these patients are deficient in glucose 6-phosphate dehydrogenase. These defective red cells can be most simply recognised by the characteristic pattern of Heinz-body formation produced in them by acetylphenylhydrazine treatment, or by their inability to retain glutathione (" glutathione instability ") after incubation with acetylphenylhydrazine (Beutler et al. 1955, Beutler 1957).

The diagnosis of favism is not likely to present difficulty if the possibility is borne in mind, but in the absence of a history of eating broad beans it may be confused with a crisis of a congenital hæmolytic anæmia. Earlier authors have denied the presence of spherocytes in favism, but their occurrence is recognised by Marcolongo, and our case could not be differentiated on morphological grounds alone from cases of congenital spherocytosis presenting with crisis. The combination of suggestive peripheral blood findings, negative direct Coombs test and maintenance of the hæmoglobin level following blood-transfusion was thought to support the latter diagnosis, but the normal result of incubation autohæmolysis excluded congenital spherocytosis and most types of congenital non-spherocytic hæmolytic anæmia. The diagnosis of favism was eventually made on the history of eating broad beans, supported by the demonstration of " primaquine sensitivity ".

On theoretical grounds it seems possible that individuals who are subject to favism may develop hæmolytic anæmia in response to certain common drugs, although little evidence to support this idea can be found in the literature apart from Luisada's observation that quinine hæmoglobinuria is rather common in patients who have previously had favism. Nevertheless favism is an indication of enzyme-defective red cells in a person, and its diagnosis may be as important as a warning to avoid certain drugs as it is a warning to abstain from broad beans.

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TOXIC MARROW FAILURE TREATED BY A HOMOGRAFT OF FŒTAL HÆMOPOIETIC TISSUE

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ENCOURAGING results have recently been reported in the treatment of disseminated mammary carcinoma with thiotepa (triethylene thiophosphoramide) combined with testosterone (Watson and Turner 1959). One of the recognised complications of this form of therapy is toxic marrow damage with peripheral pancytopenia. This complication arose in a woman with widespread metastases from a mammary carcinoma who was treated with thiotepa and testosterone at the Northern Ireland Radiotherapy Centre.

Animals exposed to otherwise lethal irradiation can be saved if injected with suspensions of hæmopoietic cells (Lorenz et al. 1951, Porter 1957, Ferrebee et al. 1958); under these conditions the injected cells " home to " and repopulate the depleted medullary cavities (Ford et al. 1956). Marrow infusions have also been successfully used in patients with marrow failure resulting from either irradiation (Thomas et al. 1959) or massive chemotherapy (Westbury et al. 1959). It was decided therefore to attempt marrow-replacement therapy in this patient by injecting homologous hæmopoietic cells. Since experiments have shown that the interactions between host and grafted homologous material are reduced if fœtal tissue is transferred (Barnes et al. 1958, Uphoff 1958), suspensions of human fœtal liver were used.

Case-report

Early in 1957 the patient, aged 43, noticed a lump in the upper outer quadrant of her left breast. When first seen, in January, 1958, the entire breast was solid with tumour and fixed to underlying muscle, and enlarged lymph-nodes were easily felt in the left axilla and left supraclavicular region. A chest radiograph revealed some lymphangitic infiltration of

the lung fields, but skeletal radiographs did not show evidence of bony metastases. Mammary carcinoma, with local infiltration and evidence of lymphatic and bloodstream spread, was diagnosed.

The patient was treated with 19-norandrostenolone phenylpropionate (' Durabolin ') 25 mg. intramuscularly once weekly for 45 weeks. The response at first was good; in March the supraclavicular and axillary nodes were no longer palpable and no discrete tumour was felt in the breast. In September the left cervical lymph-nodes had recrudesced, and the tumour was adjudged refractory to testosterone therapy.

In November oral stilbœstrol therapy (20 mg. daily by mouth) was started, but this caused considerable systemic side-effects and had to be discontinued after 3 weeks. In January, 1959, the tumour was readily felt in the breast and a palliative course of X rays was given locally to the involved area. The tumour and cervical lymph-nodes responded well, but the general condition of the patient remained poor, and it continued to deteriorate over the next 8 months.

In September the breast contained a diffuse hard mass, a chain of fixed lymph-nodes extended from the medial end of the clavicle to the mastoid process, and skeletal radiographs showed widespread bony metastases. On Oct. 1 a 5-week course of testosterone propionate intramuscularly was started; the patient was given 1000 mg. weekly in five divided doses. 6 days after starting this therapy she was given an initial dose of thiotepa 15 mg. intramuscularly, which was not followed by any reaction. 2 days later a course of thiotepa 30 mg. on alternate days, to a total dosage of 255 mg., was started. Whilst having thiotepa and testosterone therapy the patient's general condition improved initially; the mass in the breast felt softer, the cervical lymph-nodes decreased in size, and her previously severe skeletal pain decreased. Before this chemotherapy the white-cell count was of the order of 8000–9000 per c.mm., and the platelet-count was 200,000–250,000 per c.mm. When the patient had had 45 mg. of thiotepa the leucocyte-count began to fall, but despite this evidence of marrow damage we decided to continue therapy in the hope of producing maximum effect on the carcinomatous deposits. When the course of thiotepa was completed the leucocyte-count was 1300 per c.mm., and the platelet-count had also fallen, to 82,000 per c.mm. Both these counts continued to fall; 11 days later the leucocyte-count was 200 per c.mm. and the platelet-count 40,000 per c.mm. These levels were maintained for a further 5 days—i.e., until the transfusion of fœtal cells. The hæmoglobin level before chemotherapy was 11·5 g. per 100 ml., and this also fell so that on Oct. 26 it was 7·9 g. per 100 ml. The patient was then given a transfusion of 2 pints of blood, but this raised the hæmoglobin level only very temporarily, which, 11 days later, had again fallen, to 6·3 g. per 100 ml.

Attempts were not made to aspirate bone-marrow because, in view of the severe thrombocytopenia, we thought the procedure might cause excessive hæmorrhage.

The patient's general condition remained reasonably good until the end of the course of thiotepa, but from then deterioration was quite rapid. On Nov. 6 she was very weak, with severe anorexia and vomiting; she had a septic lesion on her right forehead, and extensive bruising of her legs, and she had several small hæmoptyses. At this point she was given tetracycline 250 mg. q.i.d. and methyl prednisolone (' Medrone ') 40 mg. daily by mouth.

Treatment with Hæmopoietic Cells

Next day (Nov. 7) the patient (blood-group A, CDE cde MN+ Le^a −ve S−ve K− Fy^a −ve) was given 2 pints of blood and 18 ml. of fœtal liver suspension.

The fœtal material had been obtained from a male fœtus of blood-group O, CDE cde, NS, K− Fy^a+, and stored at −78°C as described by Kay and Constandoulakis (1959). 3 ml. of fœtal material was thawed and injected into the drip at 10 A.M. at the rate of 1 ml. per min., and a further 5 ml. was injected at 11 A.M., at 6 P.M., and at 7 P.M. Chlorpheninamine maleate (' Piriton ') 2 mg. was given by mouth hourly throughout the transfusion.

No untoward reaction followed, and the patient's general condition improved quite dramatically. Her temperature remained normal, she felt better, the anorexia and vomiting disappeared, and the septic lesion on her forehead rapidly healed. She made steady progress, and was discharged home on Nov. 23—i.e., 16 days after the fœtal liver transfusion.

The immediate response in her white-cell and platelet counts is shown in fig. 1. Repeated differential white-cell counts also showed a striking change. Before transfusion the circulating white cells were all mature lymphocytes. 2 days after transfusion the peripheral blood showed myelocytes 4%, metamyelocytes 2%, band forms 40%, neutrophils 34%, lymphocytes 4%, and monocytes 16%; and there were 2 normoblasts C per 100 white cells. The neutrophils were mostly young forms, only 10% showing three or more lobes in the nucleus. Over the next 2 weeks the granulocytic series remained preponderant in the differential white-cell count; but, while the proportion of mature neutrophils increased, the myelocytes and metamyelocytes disappeared from the peripheral blood. The rise in white-cell and platelet counts has been maintained, no readings below 4000 and 200,000 per c.mm. respectively having been scored since Nov. 25.

The last blood examination on Dec. 18 showed a white-cell count of 7400 per c.mm., with a differential count of metamyelocytes 2%, neutrophils 78%, eosinophils 2%, lymphocytes 12%, and monocytes 6%; and the platelet-count was 285,000 per c.mm. The neutrophils were studied for nuclear drumstick appendages, and counts were made according to the method described by Kosenow (1956). The results were: Nov. 11, 14, and 16 male; Nov. 20 indefinite; Nov. 25 indefinite but probably female; Nov. 30 and Dec. 3 definitely female.

Immediately after transfusion and injection of hæmopoietic cells the hæmoglobin level rose to 8·6 g., at which it remained for the next 16 days (fig. 2). Reticulocyte-counts were done frequently, and the counts remained under 2% until the 8th day after transfusion; from then the proportion gradually increased until it reached 9·5% on the 16th day. From this day the hæmoglobin level rose sharply; 4 days later it was 10·4 g. per 100 ml., and the reticulocyte-count was 2%. 5 days later the hæmoglobin level had fallen to 9·8 g. per 100 ml., and the reticulocyte-count was now 9%. Since shortly after this time the hæmoglobin level has been above 10 g. per 100 ml.; the last time the peripheral blood was examined (Dec. 18) the hæmoglobin level was 10·4 g. per 100 ml. and the reticulocyte-count was 1·5%.

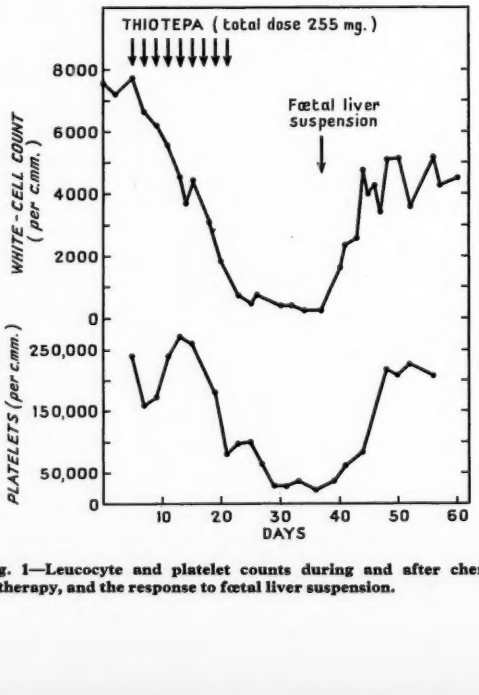

Fig. 1—Leucocyte and platelet counts during and after chemotherapy, and the response to fœtal liver suspension.

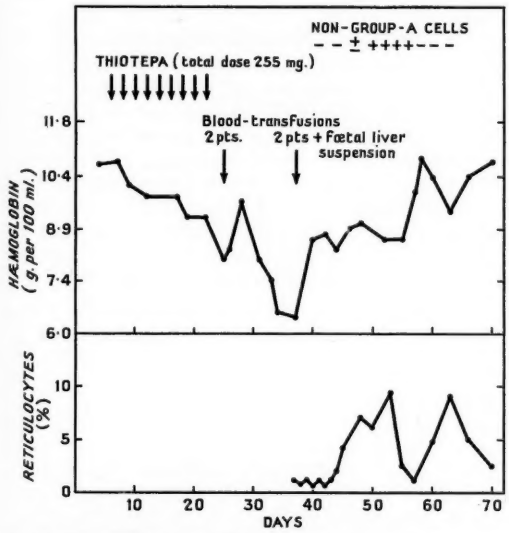

Fig. 2—Hæmoglobin level during and after chemotherapy, and the reticulocyte-response to fœtal liver suspension.

Differential agglutination of the red cells, using the modification of the Ashby technique described by Constandoulakis and Kay (1959), was done at 3-day intervals after transfusion, and showed that non-group-A cells were present 10, 13, 16, and 19 days after transfusion. On and since the 22nd day, however, this technique has not shown any non-group-A cells.

Attempts to aspirate marrow from the iliac crest were made on the 6th, 10th, and 14th days after transfusion. At the first two attempts no marrow was obtained. The third specimen showed a moderately cellular marrow, with active erythropoiesis which was normoblastic in type; and the relative proportion of proerythrocytes and normoblasts types A, B, and C was within normal limits. Granulopoiesis was active; megakaryocytes were present and undergoing normal maturation.

Radiographs of the pelvis and lumbar spine on Nov. 19 showed striking regression of the bony carcinomatous deposits.

Discussion

In cases reported by Watson and Turner (1959), which were treated with combined chemotherapy as described above, marrow damage was often observed. The number of circulating leucocytes fell to 13% of the pretreatment level (average 45% in twenty-three patients). Subsequent recovery without marrow treatment occurred within 31 days (average 11·6 days). Watson and Turner also described two cases treated with thiotepa alone in which the leucopenia persisted until they died 3 months after treatment.

More recently Gurling (1959) has reported toxic marrow damage in previously hypophysectomised patients with active mammary carcinoma who were treated by more frequent smaller doses of thiotepa. He considers that when the circulating leucocytes drop below 3000 per c.mm., or the platelet-count below 140,000 per c.mm., the drug should be withdrawn.

We thought that, in our patient, the severe anæmia (Hb 6·3 g. per 100 ml.), leucopenia (200 per c.mm.), and thrombocytopenia (40,000 per c.mm.) which persisted for 16 days after the chemotherapy was stopped made immediate spontaneous marrow recovery unlikely. We also hoped that the intense chemotherapeutic regime might have depressed the patient's immune mechanisms sufficiently to enable her to accept a graft of homologous tissue. Hence we decided to try the effect of hæmopoietic tissue transplantation.

The response to the fœtal liver transfusion was immediate and striking. The patient's anorexia and vomiting disappeared within 36 hours, a septic lesion on her forehead rapidly healed, and her general condition steadily improved. A parallel improvement was seen in the hæmatological findings; within 36 hours of the injection of hæmopoietic cells primitive granulocytes and erythroblasts appeared in the previously agranulocytic peripheral blood. The hæmoglobin level was maintained after transfusion, the leucocyte and platelet counts rose, and the pattern of the differential white-cell count changed.

There is little doubt that the transfused fœtal cells lived and matured in this patient for a time. 4 days after transfusion the circulating neutrophils were of male (donor) type, and a similar result was obtained 5 days later. On and since the 18th day, however, the circulating neutrophils have been of female (host) type. Examination of the peripheral blood for erythrocytes which were not of the same group as the host (group A) also showed that the transfused fœtal erythroblasts had matured, and that these cells were released into the peripheral circulation. Non-group-A cells were demonstrated in the peripheral blood 10, 13, 16, and 19 days after transfusion, and their number reached a maximum on the 16th day. On the same day the reticulocyte-count reached a peak of 9·5% and shortly afterwards the hæmoglobin level rose sharply (fig. 2). We think that this reticulocytosis indicated activity of the transfused fœtal erythropoietic cells. 5 days after the reticulocyte-count was 9·5% the hæmoglobin level reached a peak of 10·8 g. per 100 ml. and the reticulocyte-count had fallen to 2%. This hæmoglobin level was not maintained, falling over the next 5 days to 9·8 g. per 100 ml. Simultaneously the reticulocyte-count rose to 9%; the peripheral blood was again examined for cells of a different group from the host, but this time none were found. We think that this second reticulocyte peak indicates activity of the host erythropoietic cells.

The reversal in sex of the circulating neutrophils from male (donor) to female (host), and the absence of non-group-A cells from the 22nd day after transfusion, both suggest that the fœtal graft was not permanently accepted. Thus the patient showed chimærism for only some 3 weeks, but concomitantly with rejection of the fœtal graft her own marrow recovered and resumed hæmopoietic function.

The patient still remains well. Her left breast contains a soft diffuse mass which probably represents fibrosis resulting from radiotherapy, the cervical and supraclavicular lymph-nodes are no longer palpable, and skeletal radiographs show much improvement in the bony metastases. The peripheral blood-picture too is satisfactory, and the severe toxic marrow failure following chemotherapy seems to have been reversed successfully.

Our evidence suggests that the transplanted hæmopoietic tissue matured and survived in this patient for a time, and that its rejection was followed by restoration of normal marrow function in the host. These findings should encourage the treatment of other cases of advanced cancer by chemotherapy in maximal dosage, since toxic hæmopoietic side-effects might, as in this case, be reversed.

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A METHOD OF RECORDING SMALL MOVEMENTS

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THE most difficult task in the electrical recording of biological phenomena is often that of finding a suitable transducer. This paper is a preliminary report of our experience with a type of transducer which has recently become available* and which we find very valuable for recording tremor. It also has other applications including its use as a convenient and simple means of recording the arterial pulse.

The transducer is a titanate ceramic which exhibits a pronounced piezoelectric effect. We have used the material in the form of discs 2 in. and 1 in. in diameter and 0·02 in. thick. These were constructed by the manufacturer to respond to bending by using the two thin discs sandwiched on each surface of a central brass foil. This is a convenient way of producing a highly sensitive transducer of large capacity.

The discs used are oppositely polarised (part no. CS 648). The outer surfaces are silver-plated and may have connections soft-soldered to them if care is used. The inner surfaces are applied to a brass foil, a portion of which protrudes to form a lead. The discs may be obtained polarised in two ways so that deformation produces a charge between the outer surfaces, or between these and the central foil.

The capacity of the larger (2 in.) disc is 72,000 pf. Pen deflections of 1–2 cm. are easily obtainable with the present equipment. Because the ceramic generates a charge it is difficult to give figures for output which have any comparative value. However, the maximum overall gain of the two amplifiers is 1 cm. per deflection for 0·005 microampere current in the input circuit. At the pressures usually produced by tremor the output of the ceramic is of the order of 10–50 mV into an input load of 10,000 ohms.

In practice the performance has been satisfactory for our purposes when the ceramic has been connected to the input of a direct-current (D.C.) two-transistor push-pull amplifier designed for us by Dr. F. D. Stott.† This leads to an ink-writing oscillograph, Ediswan, which is driven by Ediswan R 2251/2 D.C. amplifiers. The records presented here were made with this instrument. However, the ceramic disc may also be connected directly to a standard D.C. oscillograph such as the Nagard D.T.103 where this type of display is indicated.

* Manufactured by Technical Ceramics Ltd., Wood Burcote Way, Towcester, Northants.

† Dr. F. D. Stott, PH.D., a member of the external staff of the Medical Research Council, at the Churchill Hospital, Headington, Oxford.

Tremor

The physiological tremor of voluntary movement in man was originally investigated by Schäfer, Canney, and Tunstall (1886), Griffiths (1888), Herringham (1890). Marshall and Walsh (1956) used an accelerometer valve (Mullard type DDR 100) to record tremor but this valve is no longer available. In our recordings of tremor, the ceramic disc (2 in.) lies on a pad of methylcellulose foam and the index finger is rested lightly on the centre of the disc. Figs. 1 and 2 show tremor recorded from the index finger with (1) the arm supported only by the shoulder-joint, and (2) the wrist supported on a firm surface. The

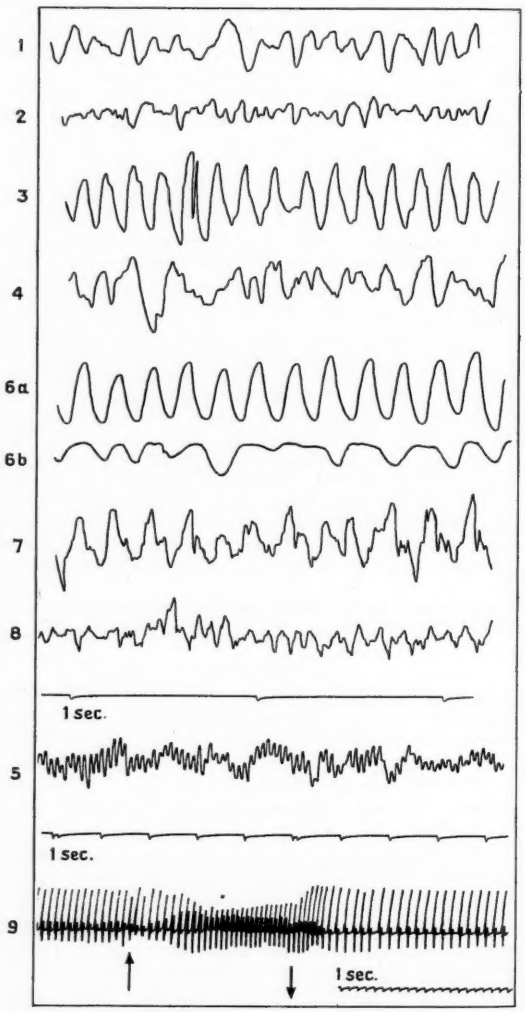

Fig. 1—Tremor recorded from index finger, wrist free.
Fig. 2—As fig. 1, but wrist supported.
Fig. 3—As fig. 1. Parkinson's disease.
Fig. 4—As fig. 1. Intention tremor in familial ataxia.
Fig. 5—As fig. 1. Familial tremor. N.B. slow paper speed.
Fig. 6a—Voluntary repeated rhythmic flexion of index finger in normal subject.
Fig. 6b—As fig. 6a, from patient with spastic ataxia; multiple sclerosis.
Fig. 7—As fig. 6a, with transducer applied over muscle.
Fig. 8—As fig. 7. Maximal voluntary effort.
Fig. 9—Transducer over brachial artery. Valsalva manœuvre. Arrows indicate duration of straining.

tremor-rate with the wrist supported is slightly greater, and the amplitude less, than without support. Figs. 3–5 were obtained, using a similar technique, from a case of parkinsonism (fig. 3), a case of familial ataxia (fig. 4) and a case of familial tremor (fig. 5). As the amplifier gain in all these records (and subsequent tremor records) was approximately the same, the amplitudes of the tremors are comparable.

Voluntary Movement

Fig. 6 shows the production of rhythmic movement by a normal subject (a) and by a patient (b) suffering from multiple sclerosis with intention tremor, with spastic weakness of the hands without posterior column loss. The instruction to the subject is to "press your finger repeatedly on the disc as evenly and rhythmically as you can".

When one is recording from the belly of a muscle, the disc is secured by an 'Elastonet' bandage wrapped gently round both disc and arm. The disc is centred on the active part of the muscle; this is determined by palpation and maximum response of the disc. Fig. 7 shows repeated small movements of the index finger, and fig. 8 shows the record obtained with isometric maximal voluntary contraction of finger flexors.

Pulse recording is most easily performed with a bender type strain gauge (Technical Ceramics type B 1), (a strip of ceramic) but a disc of 1 in. diameter has also been used successfully. This is secured over the brachial pulse in the cubital fossa with adhesive cellulose tape and the arm is extended. Fig. 9 shows a recording of the Valsalva manœuvre.

Summary

The ceramic transducer described is small, compact, and easily applied to surfaces. In addition its output is high and linear with a long time constant. These features suggest that it will have many applications in biological recording systems.

The expenses of this development were in part defrayed by a grant from the National Fund for Poliomyelitis Research.

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Medical Societies

HEBERDEN SOCIETY

Corticosteroids and Arthritis

AT a meeting held at the West London Hospital on Feb. 26 with Dr. F. DUDLEY HART, the president, in the chair, Dr. P. S. DAVIS compared some results of long-term corticotrophin treatment of rheumatoid arthritis with those of oral corticosteroids. Daily subcutaneous injections of corticotrophin gel were given to 40 patients who had not improved with rest and salicylates, and dosage was thereafter adjusted according to the clinical response and the 17-hydroxycorticosteroid output. All the patients were followed for at least two years. Treatment was discontinued in 6 because of side-effects, in 7 because of acquired resistance, and in 6 because of complete remission. Assessed by the strength of grip, the erythrocyte-sedimentation rate, and radiological appearances, the results compared favourably with those obtained with prednisolone in the Medical Research Council/Nuffield Foundation prednisolone-analgesic trial.[1] Preliminary results also indicated that corticotrophin gel caused a fall in the titre of the Rose-Waaler test in an appreciable proportion of patients, in contrast to the tendency of the titre to rise with prednisolone therapy. The relative ease of withdrawal of therapy when necessary was another factor in favour of corticotrophin gel, and injection sepsis had been negligible.

Dr. O. SAVAGE reported on side-effects during long-term corticosteroid therapy in 910 cases of rheumatoid arthritis at eight centres. The commonest were facial rounding, usually not severe; "dyspepsia", with an incidence of 32%, came next, and peptic ulceration was put at 7%. Hypertension occurred in about 13%, but in the majority of these it was not severe and only rarely was it necessary to withdraw the steroids. Other side-effects (including arteritis, peripheral neuritis, fractures and collapse of vertebræ, bruising, and mental changes) were seen in less than 5%.

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Reviews of Books

Isolated Pulmonary Stenosis

JORGEN FABRICIUS, University Hospital of Copenhagen. Copenhagen: Ejnar Munksgaard. 1959. Pp. 203. Dan. Kr. 30.

ISOLATED pulmonary stenosis, although far from the commonest of congenital cardiac abnormalities, is a lesion of great interest, for it was one of the first to be treated by direct surgery, and it is perhaps, of all congenital heart lesions, the one most accessible to assessment by special investigation. Its emergence, in twelve years, from obscurity, when even its existence was doubted by eminent cardiologists, has been remarkable. Despite the many papers already available on the subject, this monograph is a valuable addition.

Small, elegantly produced (but paper-covered), it records a study of 75 cases, all confirmed by cardiac catheterisation, and of which 23 were treated surgically. Probably no other series yet reported has been so completely and critically studied and documented. The value of the work is greatly enhanced by a thorough and critical analysis of the literature (the bibliography contains about 450 references).

Apart from a few minor vagaries, which presumably have crept in during translation, the style is precise yet readable, and conveys much information in few words. The tables and figures are well selected, clear, and informative.

It is perhaps a disadvantage that a large proportion (33 of the 75) of the patients had only *mild* stenosis (defined here as a right ventricular pressure less than 60 mm. Hg), and that only 14 had *severe* stenosis (defined as a right ventricular pressure greater than 120 mm. Hg). This has enabled the author to delineate clearly the picture of moderate and mild stenosis, but only to sketch roughly that of the surgically more important severe stenosis. This defect is, however, minor, and the monograph can be warmly recommended.

A Biochemical Approach to Pathology

M. J. R. DAWKINS, M.R.C.P., junior lecturer in pathology, University College Hospital Medical School; K. R. REES, M.SC., PH.D., senior lecturer in chemical pathology, University College Hospital Medical School. London: Edward Arnold. 1959. Pp. 128. 18*s*.

As biochemical information grows, it is becoming increasingly possible to express cell activity in terms of chemical reactions. Research in pathology has taken full account of this trend, but few of the advances have reached the standard textbooks. This book intends to offer the general reader what is otherwise to be found only in scientific journals or monographs, where it is often in highly technical language requiring specialised knowledge for full understanding.

An introduction pays tribute to Sir Rudolph Peters, who first formulated the concept of a biochemical lesion. He was able to correlate the pathology of vitamin-B_1 deficiency and of fluoroacetate poisoning with failures in single enzyme reactions. Many will be aware of the role of the vitamin in the decarboxylation of pyruvic acid, but they may find in this book for the first time a clearly written description of the jamming of the citric-acid cycle when fluoroacetate combines with oxalo-

acetate to form fluorocitrate, which then inhibits the essential enzyme, isocitric dehydrogenase or aconitase.

The chemical reactions of the cell do not proceed in isolation but in dynamic equilibrium, so that interference with one will affect the whole integrated system. Block of one energy-producing mechanism may affect all energy-producing reactions and cause immediate death. In such case the pathological changes are not specific, because there was no time for their development. Block of a side-reaction not immediately vital will disturb the integrated pattern and alter the behaviour of the cell. Disease would then represent a change in cellular metabolism brought about by pathogenic agents. The book describes reactions observed in water-soluble extracts and in " breis " which contain small particulate matter, and discusses cellular organisation and the different parts taken in chemical activity by mitochondria, microsomes, nuclei, cytoplasm, and cell wall. There are some excellent graphs and remarkable photographs. Dr. Dawkins also describes the action of poisons, endogenous and exogenous, and of bacterial toxins, and outlines the effect on cellular metabolism of deficiency in vitamins, trace elements, and essential aminoacids. The role of D.N.A. in protein synthesis and the relation of this process to the mode of gene action are explained in connection with the inborn errors of metabolism. The biochemical changes in growth, both normal and in tumours, are briefly but clearly summarised.

This book is dedicated to Sir Roy Cameron and is a worthy tribute to his progressive teaching of pathology as well as to University College Hospital Medical School from which so many pioneering contributions on this subject have come.

Back-View

Sir HAROLD MORRIS, Q.C. London: Peter Davies. 1960. Pp. 244. 25*s*.

Thomas Fuller held that " Commonly, physicians, like beer, are best when they are old; and lawyers, like bread, when they are young and new ". By this dictum, Sir Harold Morris, who cheerfully acknowledges eighty-three years, is long past his best: and it needs a biography as youthful and vigorous as this to prove that the eminent divine was sometimes wrong in his generalisations.

Sir Harold's first eight chapters are those of greatest interest to a medical reader, for they are largely concerned with his father, Sir Malcolm Morris, who was one of the first physicians in this country to specialise in dermatology. These pages describe several unusual cases, and some distinguished patients. Sir Malcolm was knighted after his successful treatment with radium of a small tumour under Edward VII's left eye. A colleague who had previously been consulted lost the Royal patronage abruptly, when an attempt to destroy the lesion by electrolysis was short-circuited by a gold chain the King wore about his neck. Conan Doyle was a close friend of Sir Harold's father and he throws fresh light on how the character and background of Sherlock Holmes evolved.

The remainder of the book deals with the author's experiences at the Criminal Bar. Yet it is in the highest degree improbable that anyone—doctor or patient, barrister or plaintiff—who once begins to read will desist until he has consumed it all.

The Anti-globulin (Coombs) Test in Laboratory Practice

I. DUNSFORD, PH.D., principal scientific officer, National Blood Transfusion Service, Sheffield; JEAN GRANT, F.R.C.P.E., director, National Blood Transfusion Service, Oxford. Edinburgh: Oliver & Boyd. 1959. Pp. 120. 12*s*. 6*d*.

A CONSIDERABLE literature has accumulated in the fifteen years since this test was introduced to hæmatological laboratories, and many variations of the original technique have been suggested. This essentially practical handbook sets out in minute detail the techniques the authors now think best. This practical instruction is preceded by a short account of the theory of antibody-antigen reactions and of the historical development of the technique. The difficulties and false reactions met with in regular use of the test are fully discussed; and there is a description of applications in fields other than blood-grouping and hæmolytic serology. This little book is a useful account of current techniques, and although refinements of technique go on all the time, it is valuable to have a standard that need not be altered until some major rearrangement is necessary.

Low Intensity Radium Therapy

CHARLES L. MARTIN, M.D., F.A.C.R., clinical professor of radiology; JAMES A. MARTIN, M.D., F.A.C.R., assistant professor of radiology, South Western Medical School, University of Texas, Dallas. London: J. & A. Churchill. 1959. Pp. 277. 90*s*.

THIS volume is written by father and son, whose work over the past thirty years provides the material for the book, and as the title suggests, their therapy has evolved round interstitial radium techniques.

There are two parts to the book. Part 1 deals with technical considerations, including a very readable opening chapter on the history of radium—a novel in itself. The system of dosage as evolved by Edith Quimby is described: it is easy to comprehend and simple to apply, and, as the authors remark, the good results seem to justify this plan. Part 2 is concerned with clinical material, presented in case-history form, and lavishly illustrated with pre- and post-therapy photographs and a diagram to show the radium implant pattern for all cases. There are over 100 illustrations, not counting an excellent colour atlas.

To most therapists in this country, brought up on the Parker-Paterson dosage system, many of the implants may seem strange, but the authors are clearly artists in their work, and the justification of their work is in their excellent results. Very few people still treat carcinoma of the cervix with radium needles, and implantation of the intercostal spaces after radical mastectomy for carcinoma of the breast cannot have many disciples left.

This is a very readable and stimulating book, but the student should hesitate before quoting from it, in case his examiners object to some of its " heresy ".

British Surgical Practice (*Surgical Progress 1959*. London: Butterworth. 1959. Pp. 479. 52*s*. 6*d*.)—The 9th progress volume of *British Surgical Practice* is of particular excellence in a series which is well known for its quality. It follows the usual arrangement, consisting of 20 articles reviewing various aspects of surgery, each followed by abstracts of the relevant outstanding papers of the previous year. Sterilisation by heat, peptic ulcer, partial hepatectomy, chronic pancreatitis, rectal surgery, parotid tumours, endocrine surgery, breast cancer, amputations, and flexor tendon injuries are the titles of perhaps greatest interest to general surgeons; but orthopædic, gynæcological, neurosurgical, ophthalmological otological, and radiotherapeutic topics also receive attention, and an article on progress in the casualty department brings up the rear. The " noter-up " keys the contents of this and preceding progress volumes to the chapters in the original work. For any surgeon who finds difficulty in keeping up with the literature (another way of saying all surgeons) this volume is prescribed reading, and it is to be hoped that Sir Ernest Rock Carling and Sir James Paterson Ross will not find tedium in the repeated congratulations and thanks of surgeons for the excellence of their editing.

Cancer in Families (Cambridge, Mass.: Harvard University Press, for Commonwealth Fund. London: Oxford University Press. 1959. Pp. 76. 20*s*.).—This monograph by Prof. Douglas P. Murphy, of the University of Pennsylvania, and Dr. Helen Abbey, of Johns Hopkins, reports an investigation into the incidence of cancer in relations of individuals with breast cancer. 200 families were involved and the survey was of necessity retrospective. Data were obtained by interview, and three of the four interviewers were trained nurses. This serious statistical study revealed no detectable familial tendency towards cancer.

THE LANCET

LONDON 19 MARCH 1960

Orthostatic Hypotension

ORTHOSTATIC hypotension may be the consequence of an obvious lesion, or on the other hand it may be unassociated with any discoverable nervous or systemic disorder. The condition may give rise to nothing worse than an endurable dizziness on standing, or, by contrast, to a state in which the patient hurries from chair to chair in a crouching position to avoid fainting.[1] The excessive fall in blood-pressure when the upright posture is assumed is due to failure of the normal compensatory vasoconstrictor reflexes. In mild cases some patients complain of tachycardia, besides giddiness, on standing; but others do not have the tachycardia, which clearly compensates partly for the fall in blood-pressure. The condition may progress no further, or its severity may increase insidiously and other disabilities appear. The disorder is always worse in the heat, when the vascular bed is normally enlarged owing to cutaneous vasodilatation. Sweat production may fail, though the specialised axillary glands may be spared; difficulties in micturition and defæcation may develop; there may be diarrhœa or constipation; some patients complain that mastication causes pain and swelling in the parotid gland; and commonly erection becomes impossible.[2-4] All these disturbances are clearly related to activity of the autonomic nervous system. The common complaints are due to sympathetic dysfunction, but the parasympathetic system may also be involved; and the manifestations must depend on the degree of involvement of one or both parts of the autonomic nervous system. Examination of the patient with orthostatic hypotension of autonomic origin usually reveals no abnormality of the somatic or central nervous systems, and no concurrent disease such as adrenal cortical hypofunction. In many cases the patients present in middle or old age with a history of some disability, weakness, and fatigue for a considerable time. On the other hand, the disease may manifest itself after some stress such as pregnancy[1] or spinal anæsthesia.[4] In one young man the onset apparently took place during an undiagnosed illness in which faint generalised erythema had been present.[3] There seem to be no pathological reports on patients who had the disease.

With the patient recumbent the blood-pressure is usually in the normal range: only when he sits or stands does his abnormality become obvious. Experiment supports the guess that the sympathetic (and parasympathetic) nerves are at fault. In health, blood and urinary adrenaline and noradrenaline increases with a change from the horizontal to the vertical position, either actively or passively by tilting.[5] This is a quantitatively measurable sign of increased activity of the sympathetic nerves, which release noradrenaline at their vasomotor endings and adrenaline from the adrenal medulla. In patients with postural hypotension there is little or no increase in the blood and urinary concentration of these catechol amines[5]—a clear indication of failure somewhere in the chain of events leading to necessary vasoconstriction. A similar absence of rise in noradrenaline concentration is found after sympathectomy.[6] Parasympathetic involvement is demonstrated by failure of hypoglycæmia to increase gastric acidity, absence of change in pulse-rate on administration of atropine, and absence of bradycardia in response to administered adrenaline[4]; massage or compression of a carotid sinus evokes no change in pulse-rate or blood-pressure when the parasympathetic inhibitory nerves to the heart are functionless.[4] These are not the only demonstrable signs of autonomic imperfection. Withdrawal of blood or the administration of an intravenous infusion leads to an exaggerated fall or rise of blood-pressure owing to the failure of reflex mechanisms which normally and rapidly damp the effect of volume change by constriction or dilatation of visceral, muscular, and cutaneous vessels.[3] Another sign of functional sympathectomy is hypersensitivity to pressor agents: thus an excessive rise in blood-pressure follows injection of a small dose of adrenaline, and as little as 10–20 milliunits of vasopressin as a single injection, or an infusion of 1 milliunit per minute, may induce a rise in blood-pressure.[3] Normal people show little pressure change after far larger doses of vasopressin,[7] even when these are great enough to produce visible paling of the skin; but after administration of a ganglion-blocking agent normal people respond like patients with postural hypotension.[4] (In a young patient whose renal function was examined, the response to an infusion of normal saline solution resembled somewhat that of many four-footed animals whose vasoconstrictor system is less sensitive than that of man with his upright posture. The patient responded with a rapid urine flow, a high rate of loss of sodium, and an increase in glomerular filtration-rate.[3] Normal people maintain a steady glomerular filtration-rate even after such an infusion, and lose the excess water and sodium far more slowly.)

Some of the various suggested causes of this disorder —for instance, inadequate return of venous blood to the heart,[8] and an abnormally great reduction of blood-volume on standing[9]—are probably in fact consequences of autonomic dysfunction. Where sympathetic activity is low or absent the arterioles and capillaries will lack tone, blood will pool easily, and the capillary walls will

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be more than usually permeable to plasma. A lesion giving rise to these effects could lie at one or more of several sites. In their article last week Professor SHARPEY-SCHAFER and Dr. TAYLOR [10] reported instances of orthostatic hypotension in patients with diabetic neuritis and showed that in this condition, even when it is severe, absence of circulatory reflexes was by no means inevitable. But where the reflexes were absent the efferent vasomotor pathway was intact, as was shown by normal vasodilatation to indirect heating, and normal constriction of finger vessels on taking a deep breath. These workers conclude that in diabetic neuritis, as in tabes, the lesion lies on the afferent side of the reflex arc. But in the instances of "pure" or "simple" orthostatic hypotension which have been discussed here it is not clear where the lesion lies, nor what it is. In some cases, as in diabetic neuritis, apparently normal vasomotor responses can be elicited by pinching the skin—an indication that the peripheral part of the vasoconstrictor nerves is intact.[11] In other cases a normal response can be obtained in the upper but not in the lower limbs.[11] The only explanation is that painful stimuli may share a final common path with the postural reflexes, but must take a different route somewhere. On the other hand, the fact that the disorder can be progressive and ultimately affect both parts of the autonomic system points to some central lesion.

Since we are ignorant of the origin and pathology of this disease, treatment has to be symptomatic. The mildest cases may be much helped by elastic stockings and body-belts. In the more severe cases, without such mechanical aids the patient may faint on standing. If he falls flat, perhaps not much harm will be done; but if he falls in such a way or place that he is not flat, then he may die of cerebral anoxia before help comes. Theoretically any agent which raises the blood-pressure may be useful, for the simple reason that when the patient stands, although the proportional fall of blood-pressure may be as great as before, the lowest level is above that which leads to cerebral anæmia. In this way the most disabling feature of the disease is moderated; but the disease is not cured, as is evident from the persistence of other symptoms such as hypohidrosis and failure of erections.[2-4] With vasoconstrictors the difficulty is to find one with a long action which does not induce tolerance or have undesirable side-effects. With the adrenaline-noradrenaline type of drug the benefits are on the whole short-lived or produce, among other things, harmful local reactions due to the very vasoconstrictor effects for which they are administered.[1] Another approach is to raise the blood-pressure by increasing the blood-volume; and success has been reported from administration of deoxycortone acetate in oil with extra sodium chloride in the diet.[1] (Clearly any patient receiving a combination of deoxycortone acetate and salt must be under regular supervision.) Recently 9-α-fluorohydrocortisone in doses considerably below those affecting the carbohydrate-regulating system has been found beneficial.[2] One great advantage of this substance is that it can be given by mouth. But, as with all other treatments, the basic defect remains; for when the patient stands the plasma-noradrenaline does not rise as it should.

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Favism

FAVISM, "a singular disease chiefly affecting the red blood-cells", has been known for centuries since affected persons lived originally in the Mediterranean basin. In modern times it has been most prevalent among the inhabitants of the island of Sardinia, with lesser groups in Sicily and Southern Italy [1]; but in the past twenty years cases in other areas have come to light. The disease is due to sensitivity to the ingestion of the broad bean (*Vicia faba*) or to inhalation of the pollen. FERMI,[2] who recorded 1211 cases of the disease in 1905, found that 38% of the attacks were due to inhalation and 62% to ingestion. LUISADA [1] pointed out that intake of a single seed can cause the syndrome, and attacks have been brought on by drinking water in which fava leaves have been kept or by drinking milk from a goat that has been fed on broad-bean plants. The syndrome is the same whether brought on by inhaling pollen or by eating beans, but the pollen produces an attack within seconds whereas some hours elapse after eating beans before symptoms appear. The first symptoms are dizziness, headache, nausea and vomiting, lumbar pain, and pyrexia, but in five to thirty hours the characteristic hæmoglobinuria and jaundice appear. The urine varies from red to black; the jaundice is intense; and sooner or later pallor due to increasing anæmia appears. The hæmoglobinuria and fever usually clear up by the fifth or sixth day; the jaundice persists somewhat longer; and the anæmia, if untreated, may still be present up to a month later. The attacks are rarely fatal except in children, in whom the mortality may reach 8%. Blood examination shows reduction of red cells to between one and two million per c.mm.; there is pronounced leucocytosis, reticulocytes rise to as much as 30–60%, and in fact the picture is that of acute hæmolytic anæmia. The red-cell fragility is usually normal, the Donath-Landsteiner reaction is negative, and the Coombs antiglobulin test has been found to be negative.

Cases of favism have now been reported from other parts of the Mediterranean littoral and from countries to which Mediterranean inhabitants have migrated. MANSOOR [3] reported 2 cases from a single village in Israel. A case was reported in the U.S.A. by MCCRAE and ULLERY [4] in 1933, and there have been others since. MCCARTHY [5] described a case in a 9-year-old boy admitted to hospital in Chichester; the boy's parents were of English descent as far as was known. DISCOMBE and MESTITZ [6] described a case of favism after a meal of broad beans in an English-born child whose parents' families both came from Baghdad. DISCOMBE and MESTITZ pointed out that the so-called "Baghdad spring anæmia", said to be due to the inhalation of the pollen of spring flowers, is very similar to favism. Other

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plants now known to cause a similar syndrome include the stinkwood, the bog-bilberry or whortle-berry, a mushroom (*Morchella esculenta*), male fern, and a pea (*Pisum sativum*).

Favism, and presumably the similar syndromes, is regarded as of allergic origin, and the protein of *Vicia faba* has been clearly shown to provoke an attack of hæmolysis with accompanying hæmoglobinuria and jaundice in a sensitive patient. But we have only recently learnt what the abnormality in the red cells is that makes the patient sensitive to these proteins. In January we drew attention to a new familial abnormality of red blood-cells [7]; in this condition the red cells are deficient in the enzyme, glucose-6-phosphate dehydrogenase, and this deficiency appears to be the basis of some unusual drug-sensitivities causing hæmolysis. The defective red cells can be recognised by a test devised by BEUTLER et al.[8] The red cells are suspended in a heparin-containing phosphate buffer of pH 7·6 to which has been added glucose 200 mg. per 100 ml. of the reducing-substance, acetylphenylhydrazine, 100 mg. per 100 ml.; the mixture is incubated for four hours, and wet preparations are then made and stained with cresyl-violet. In a sensitive person five or more Heinz-bodies appear in more than 40% of the red cells. Another method is to demonstrate the inability of the abnormal red cells to retain glutathione in the presence of reducing agents.

This enzyme abnormality of red cells has been demonstrated in cases of favism by workers in Italy and Israel.[7] In this issue Dr. GOWER and Dr. FROMMER describe a case, seen in London, af a 3-year-old Cypriot child with the typical hæmoglobinuria and icterus. On the first admission the cause of the syndrome was not detected; but when, eight months later, he was re-admitted with the same syndrome, a history of eating broad beans was obtained. The child recovered rapidly without needing blood-transfusion, and later, when his red cells were investigated by the Beutler Heinz-body test, 80% of his cells developed multiple Heinz-bodies. A modern twist to this story is given by the fact that the attack occurred in the month of March. In Sardinia the disease is strictly seasonal; the inhalation cases occur in April and May when the *Vicia faba* plants blossom, and the ingestion cases occur between May and August when the beans are fresh. But in London broad beans can be bought out of the deep-freeze and so favism may develop at any time of the year.

This case in a Cypriot immigrant and occasionally in others in Great Britain should remind us to include favism in the differential diagnosis of unexplained attacks of hæmolysis and hæmoglobinuria. We now have a test for detecting the abnormal red cells, and need not go to the length of precipitating an attack with a test dose of broad beans. And since favism and similar syndromes are so easily avoided, the diagnosis should be made whenever possible. Favism is well known to be a familial abnormality, so tests among the patient's family are often rewarding.

7. *Lancet*, Jan. 2, 1960, p. 37.
8. Beutler, E., Dern, R. J., Alving, A. S. *J. Lab. clin. Med.* 1955, **45**, 40.

Annotations

MATERNITY-HOSPITAL REPORTS

FOR many years it has been the custom in this country and in the Commonwealth for leading maternity hospitals to produce an annual account of their work, but rising printing costs and changes in obstetric practice make it necessary to review the form and value of these reports. In the first quarter of this century they followed the example set by Dr. Charles Longridge, of Queen Charlotte's Maternity Hospital, London. In 1928 the obstetric section of the Royal Society of Medicine suggested a standard plan, which was widely used until the Royal College of Obstetricians and Gynæcologists, in 1948, recommended a number of changes. Two years ago the college, in the interest of economy, suggested that hospitals should continue to draw up the standard report, but for general distribution should prepare a brief statistical summary. Few hospitals so far have put this recommendation into practice, but it seems likely that in time most will do so.

A certain amount of variation and experiment is evident in recent reports. The last three from the Simpson Memorial Maternity Pavilion, Edinburgh, have been largely in summarised form, and, like that from the Mill Road Maternity Hospital in Liverpool, have been favourably received. In an attempt to stimulate standardisation the Edinburgh reports now have an appendix with a comprehensive list of definitions. G. T. D. Barr, in his brief statistical analysis of the work of the Princess Mary Maternity Hospital, Newcastle upon Tyne, in 1957, has included a critical review by Dr. William Walker of the hospital's experience of rhesus immunisation between the years 1948 and 1958. This hospital, in its annual reports, intends to produce from time to time an account of the hospital's management of some obstetric or pædiatric problem.

The Rotunda, the Coombe, and the National hospitals in Dublin continue to produce detailed yearly reports, and for several years these have been discussed at special meetings of the Royal Academy of Medicine in Ireland. Last year Prof. R. J. Kellar, as guest speaker, on the whole welcomed such reports, provided they were properly prepared, and he thought that they served a useful purpose.[1] Some obstetricians would question this view. In former years they drew attention to the considerable maternal mortality and morbidity associated with childbirth; but this need has largely passed, and today there are more effective and less expensive means of studying maternal deaths.[2]

Whether these reports can contribute to our knowledge and understanding of perinatal mortality is arguable. Generally the information contained in them lacks the clinical and pathological precision required for serious study, and, owing to differences in methods of recording, one report cannot readily be compared with another. Most hospital populations are heavily selected, and the true incidence of the various complications which may threaten the life of the child cannot be established. A comparison of hospital reports will never explain why, in this country, perinatal mortality is higher in the North than in the South and in industrial than in rural areas. Before we can understand the social and medical factors which together are responsible for these differences we

1. *Irish J. med. Sci.* 1959, **408**, 529.
2. Report on Confidential Enquiries into Maternal Deaths in England and Wales 1952–1954. H.M. Stationery Office, 1957.

must define and compare total communities. This was hinted at in the Cranbrook Committee's report [3] when a plea was made to extend hospital clinical reports, with the help of the local authority, to cover the domiciliary midwifery service in the area.

In defence of annual clinical reports it may be said that collection and presentation of the material is good training for registrars and housemen. But the filling in of a standard form by junior medical staff must not be mistaken for a dependable records system. Much more is required. The consultants must set the standard and be prepared to supervise the quality of case-note taking, and themselves take part in transcribing medical information from the case-notes into the records system. Definitions must be discussed and agreed on. The success of any records system depends primarily on the quality of the information fed into it. To match this effort on the part of experienced medical staff, there must be an efficiently organised records department.

The prestige value of annual maternity reports should not be allowed to weigh too heavily. The time is opportune for administrative officers, as well as obstetricians, to look carefully at this matter and to decide whether reports in their present form justify the expenditure. Of the various alternatives, a relatively simple regional maternity report has much to commend it.

INDIAN TUBERCLE BACILLI

THE response to infection by tubercle bacilli differs between races. Such differences are found in mixed communities—for example, the Malays and Chinese in Singapore and the white and Negro races of the United States—so it seems likely that the major factor is in the hosts and not in the bacilli. But some clinicians have thought that in addition the virulence of strains of tubercle bacilli may differ in different parts of the world; the idea was apparently based on alleged differences between the disease in Europeans infected in the East and the disease in those infected in their own countries. There has been little bacteriological support for these speculations. Although strains of tubercle bacilli have long been known to differ in their virulence for laboratory animals, there was no acceptable evidence that the pattern of virulence among the strains differed in one country from that in another. In India there was a suggestion that a proportion of the strains isolated from patients were less virulent for guineapigs than European strains [4–6]; but accurate estimation and comparison is difficult, requiring careful design and execution of the experiments. A cooperative investigation has now firmly established differences of virulence between strains obtained from patients in Great Britain and in South India.[7]

83 South Indian and 29 British strains of *Mycobacterium tuberculosis* were studied in two laboratories in Britain and one in Madras. All were sensitive to streptomycin and isoniazid. About three-quarters were tested by the niacin test, and all were shown to be of human type. Three strains of guineapig were used—one bred in London, one in Madras, and the third in both places. Virulence was assessed by the amount of disease found in the animals six and twelve weeks after infection, the amount being expressed by an arbitrarily defined method of scoring. The best measurement of virulence was found to be the "mean index"—the score divided by the survival-time of the animals. The Indian cultures were found to have a wider range of virulence than the British, and only about 30% of them were as virulent. The least virulent of the Indian strains caused little more than local lesions. In one experiment, using guineapigs bred for several years in Madras, the "mean index" from 24 Indian strains was 0·68 and from 11 British strains 1·64; in another, using guineapigs bred in London, the "mean index" from 8 Indian strains was 0·48 and from 6 British strains 1·23. Full analysis of the whole series of experiments showed that the findings had "with little doubt" been uninfluenced by the breed of animal, differences of diet, or technical errors. The authors wisely emphasise that their results apply only to strains isolated from poor patients living in Madras city, and that there is no evidence that the Madras strains are less *infective* than British strains, although many of them are less *virulent* in the guineapig. They point to the paradox that in India, although there is apparently more human tuberculosis than in Britain, it is caused by bacilli of lesser virulence to animals; and they suggest a reasonable hypothesis.

Tubercle bacilli are mainly spread by patients with chronic cavitating disease. The level of virulence that is of the greatest survival value to the bacilli is, therefore, the one that most commonly causes this type of disease. In a country such as Britain, where the risk of infection is falling and the people are well nourished, attenuated strains may be unable to establish sufficient chronic cavitating tuberculosis to survive; and in these circumstances, high virulence has the greatest survival value. On the other hand, where risk of infection remains high and the people are ill-nourished, as in the particular population studied in Madras, attenuated strains may more often be able to cause chronic cavitating disease and continue to exist. "Attenuation may therefore be a modification imposed on the bacilli by the need to establish the correct balance between the susceptibility of the host and the virulence of the parasite."

BELL'S PALSY

WHEN a peripheral nerve rapidly becomes blocked and ceases to conduct, the neurologist's first thought is that the nerve has been compressed or stretched in some way, and this may of course involve some interference with the blood-supply to the nerve. The facial nerve traverses a bony canal and is supplied by very small arteries, one of which is a branch of the external carotid artery and enters the stylomastoid foramen to supply the nerve. It is not surprising therefore that many have considered that in Bell's palsy the facial nerve must either be compressed by œdema in the facial canal or else have its blood-supply interfered with, or that perhaps it suffers from a combination of both processes. In any event it is reasonable to try the effect of therapy which will counter such processes.

Korkis [1] reports remarkable success from stellate-ganglion blocks with 1% procaine solution, repeated, if necessary, every three days: such blocks were applied one to four times, the average being two. Of 20 patients with complete paralysis, 16 recovered completely within three weeks: the 1 patient who did not recover fully was

3. Report of the Maternity Services Committee. H.M. Stationery Office, 1959.
4. Dhayagude, R. G., Shah, B. R. *Indian J. med. Res.* 1948, **36**, 79.
5. Frimodt-Möller, J., Mathew, K. T., Barton, T. M. *in* Proceedings of the 13th Tuberculosis Workers Conference, p. 157. Tuberculosis Association of India, New Delhi, 1956.
6. Singh, B. Technical Report of the Scientific Advisory Board, p. 158. Indian Council for Medical Research, New Delhi, 1957.
7. Mitchison, D. A., Wallace, J. G., Bhatia, A. L., Selkon, J. B., Subbaiah, T. V., Lancaster, M. C. *Tubercle. Lond.* 1960, **41**, 1.

1. Korkis, F. B. *A.M.A. Arch. Otolaryng.* 1959, **70**, 562.

not treated until twenty-three days after the onset. The results in cases of incomplete facial paralysis were very striking in that improvement was almost immediate. Latterly Korkis has combined stellate-ganglion block with administration of prednisone.

Any such measures are of course most likely to succeed if they are applied soon after the onset; and in this series treatment was usually started within a day or two after signs appeared.

These results are so good that the method should be tested by others. It is difficult to see how it can do any harm, and some serious disfigurements may be avoided.

RADIOGRAPHIC DETECTION OF PRIMARY PEPTIC ULCER

THE mere exhibition of a dose of barium sulphate and exposure of radiographs is, it seems, commonly expected to decide whether a dyspeptic patient has a peptic ulcer. This belief is implicit in case-reports which read " barium-meal examination showed . . .", as though the examination was self-controlled and at its conclusion the X-ray screening-couch presented an appropriately labelled ticket. Certainly the demonstration of a peptic ulcer can be one of the simplest exercises in radiology, but quite often it is one of the most difficult.

The radiological diagnosis of any lesion depends on two factors—demonstration and recognition. The ease with which an ulcer is demonstrated depends on its size, its site, and the presence of any obscuring associated or unassociated lesion. If an ulcer is less than 2 mm. in diameter it is unlikely to be demonstrated even when it is in one of the sites where ulcers are most readily detected—namely, the middle third of the lesser curvature of the stomach and centrally on the anterior or posterior wall of the duodenal cap. Much larger lesions involving only superficial erosion of the mucosa cannot be shown radiologically. Few organs have a wider range of shape, size, and situation than the normal stomach. Various degrees of rotation on both longitudinal and transverse axes are encountered, and in some cases the word " axis " has no real meaning since the rotation is so bizarre. Detection of an ulcer on the upper part of the posterior wall of a stomach of this kind may be extremely difficult. Normal rugal pattern seen in profile can simulate ulceration; out-pouchings of mucosa in the cascade type of stomach are deceptive; and small gastric diverticula, though less confusing, may give rise to trouble in interpretation. Ulcers in the roof of the antrum have an unfortunate knack of trapping fluid when the patient is erect, and unless carefully sought with the patient prone they may be missed even when they are of considerable size. Juxta-pyloric gastric ulcers may be obscured by spasm or fibrotic contraction of the antrum. Ulcers on the middle third of the lesser curvature are usually easier to detect, but even here confusing and fallacious appearances of deep ulceration may be found [1 2] when the actual lesion is no more than a superficial erosion. A gastric ulcer in a large hiatus hernia (which may contain stomach, duodenal cap, and perhaps part of the colon as well) may be almost impossible to demonstrate, on account of gastric volvulus. When the stomach is already scarred and deformed by old-standing ulceration, the detection of present ulceration may be especially difficult.

The distinction of simple from malignant ulceration in the stomach is at times impossible: if the surgeon and morbid anatomist with the affected tissue between their fingers can sometimes only guess, the radiologist is hardly to be blamed for some errors. Nevertheless, when the experienced radiologist confidently diagnoses a simple ulcer, he is seldom wrong.[3] The mere size of the ulcer crater is not a reliable guide. Robbins,[4] in a consecutive necropsy series of 190 benign and 68 malignant ulcers, found that of those with a crater diameter of more than 4 cm. 20 were simple and 33 malignant; this is unlikely to indicate the full incidence of large simple ulcers since such cases are often treated satisfactorily and do not appear at necropsy. Large size is an embarrassment to the radiologist since he cannot easily apply the criterion of ulcer projection from the gastric outline (probably the most accurate indication of simplicity) to an ulcer which has destroyed more than a quarter or a third of the gastric contour from which its projection is to be judged. Carman's [5] meniscus sign can certainly be found in simple ulceration. Location of the ulcer in the antrum or on the greater curvature, though increasing the likelihood of neoplasia, is no positive indication of this.

Duodenal ulceration is much more often obscured by accompanying scar deformity than is gastric ulceration. In many patients the first and second parts of the duodenum cannot be kept under the same continuous controlled observation as can parts of the stomach. The duodenal contents may be propelled rapidly and the duodenal cap may remain empty—the terms " irritable " and " spasm " are probably a measure of the radiologist's frustration as well as of the behaviour of the duodenal cap. Considerable ingenuity and practice may be needed to satisfy the orthodox radiographic principle of obtaining at least two views at right-angles to each other of the part examined: prone and supine views with and without compression and air contrast relief patterns [6] may be needed. It may be even more difficult to establish the existence of an ulcer in a grossly deformed duodenal cap in a patient with a long history than to exclude the presence of an ulcer in a patient with a history of only a fortnight's dyspepsia. Paterson and Hancock [7] have illustrated some of the difficulties in correlating the radiographic appearances of duodenal ulcer with the surgical findings shortly afterwards. They note that ulcers may appear as polyp-like filling defects in the duodenal cap owing to the œdema around the crater preventing or almost preventing the crater being filled with barium. In some patients the whole of the duodenal cap is replaced by an ulcer which appears so large and symmetrical that it may be mistaken for a normal duodenal cap.[8 9]

Postbulbar duodenal ulcers present difficulties of their own.[10 11] They arise as a rule in well-nourished hypersthenic men in whom the duodenal cap may be quite normal and when filled completely obscures the site of ulceration immediately beyond. These ulcers, missed by routine radiographic examination, may be undiscovered at laparotomy since they are usually in the medial and posterior wall of the upper part of the descending duodenum in a most inaccessible region for direct

1. Moutier, F. *Pr. méd.* 1932, **34**, 681.
2. Lundie, J. K., Scott, M. G., Mackenzie, D. H. *Brit. J. Radiol.* 1955, **28**, 95.
3. Doll, R., Avery Jones, F., Pygott, F., Stubbe, J. L. *Gastroenterologia*, 1957, **88**, 1.
4. Robbins, S. L. *J. Amer. med. Ass.* 1959, **171**, 2053.
5. Carman, R. D. *ibid.* 1927, **77**, 990.
6. Hampton, A. O. *Amer. J. Roentgenol.* 1937, **38**, 565.
7. Paterson, D. F., Hancock, D. M. *Brit. J. Radiol.* 1960, **33**, 43.
8. Dawson, J. *ibid.* 1958, **31**, 666.
9. Pygott, F. *in* Modern Trends in Gastro-enterology (edited by F. Avery Jones). London, 1958.
10. Kaufman, S. A., Levene, G. *Radiology*, 1957, **69**, 848.
11. Cooke, L., Hutton, C. F. *Lancet*, 1958, i, 754.

surgical palpation; they often bleed, and they often are associated with severe back pain which in some instances has provoked exploration for non-existent lumbar disc lesions.

Appearances mimicking simple duodenal ulceration are sometimes produced as the result of extrinsic involvement by tumours—notably from the pancreas and gall-bladder. Mimicry may be exact, since duodenal ulceration of a sort is present and the deformity due to fibrotic contraction round a simple ulcer is counterfeited by infiltration and contraction due to neoplastic involvement.

Rarely, simple peptic ulceration is found in the distal duodenum or jejunum.[12–14] Here the ulcer crater may be obscured by associated " duodenitis " or " jejunitis ".

What, then, is the place of radiology in the diagnosis of peptic ulcer? It is certainly not an exclusory method of examination. A barium-meal examination is undertaken to show an ulcer, and if one is demonstrated its existence is proved; but the ulcer may be there even when careful search has failed to reveal it. The advantages of the radiological investigation lie in its scope—the opportunity to demonstrate independent but not necessarily irrelevant lesions such as gallstones, hiatus hernia, pancreatic tumours, small-intestine disease, and even supradiaphragmatic abnormalities. In competent hands accuracy of diagnosis is great, but just how great it is impossible to say under the conditions of clinical practice. The detection of a lesion is easier than its diagnosis in terms of histology. Occasionally radiological interpretation is correct even when the gastroscopic and surgical findings have run counter to it. Periodic radiological observation of, say, a gastric ulcer may indicate that continued medical treatment is unlikely to achieve more than palliation.[15 16] Certainly the radiologist who plays a lone hand without close support by clinician and pathologist will make many mistakes; but equally certainly as a member of a team his honest endeavour will provide a full share of aid in the elucidation and treatment of one of the commonest ills to which modern flesh is subject.

HISTORY AND THE PARASTERNAL LYMPH-GLANDS

" Dr. W. H. Cushing, my house surgeon, has in three instances cleaned out the anterior mediastinum on one side for recurrent cancer. It is likely, I think, that we shall in the near future remove the mediastinal contents at some of our primary operations." This could almost have been put to a medical panel in a radio transatlantic quiz of the type which is now becoming popular at some scientific meetings: and shame on the doctor, American or British, unable to identify the author as Halsted.[17] The question-master would probe further before awarding three marks. The topic? Breast cancer—one more mark. The point of specific interest? That here is the first known record of interest in the spread to the internal mammary lymph-glands of cancer from the breast. The next quotation to be identified by the panel might well be: " The following cases, the notes of which have been prepared by my registrar, Mr. D. H. Patey, illustrate the control of sternal recurrence in breast cancer, sometimes for years, by buried radium treatment, with relief of pain, disappearance of the swelling, and healing of the ulceration if present." And shame to the British side at least if they could not recognise the voice of Sampson Handley.[18] Handley had stimulated Stibbe to undertake anatomical dissections which revealed lymph-nodes at a plane anterior to the internal mammary artery opposite the upper three and the sixth intercostal spaces [19]—work which has been substantially confirmed by Urban,[20] whose researches reveal only a slight variation in incidence in comparison with the figures given by Stibbe. Handley the elder acted on this anatomical knowledge and placed his radium needles in the appropriate spaces. His son,[21] carrying researches further, showed that almost a third of 139 patients with " operable " breast cancer had invasion of the internal mammary chain, involvement being three times greater in medially than laterally placed growths; internal mammary metastases were present in over two-thirds of growths situated medially in the breast.

These findings have posed a therapeutic problem which some have attempted to solve surgically [20 22] (Wangensteen [23] fulfilling the hopes which Halsted voiced for his own technique [17]) and others radiotherapeutically. It has proved difficult to deliver an adequate dose of X-irradiation in the area without damaging structures in close proximity [21]; but Smithers and Rigby-Jones [24] have now developed a technique which permits irradiation of the internal mammary nodes (or parasternal in their nomenclature) of patients with cancer in the medial half of the breast and of those with laterally placed lesions in whom the axillary glands are involved. Lest it should be thought that attention paid to this area when so wide a lymphatic field is at risk savours of straining at a gnat, it is worth recording that one of Sampson Handley's patients submitted to radical mastectomy in 1923 at the age of 37 developed a recurrence in the second parasternal space which he treated with a radium implant. This was the first patient he treated thus; and she survives today, 37 years later, without further recurrence.

12. Forty, F., Barrett, G. M. *Brit. J. Surg.* 1952, **40**, 60.
13. Zollinger, R. M., Ellison, E. H. *Ann. Surg.* 1955, **142**, 709.
14. Summerskill, W. H. J. *Lancet*, 1959, i, 120.
15. Doll, R., Pygott, F. *ibid.* 1952, i, 171.
16. Scott, W. G., Loitman, B. S., Swanson, H. A. *J. Amer. med. Ass.* 1959, **171**, 2048.
17. Halsted, W. S. *Ann. Surg.* 1898, **28**, 557.
18. Handley, W. S. *Clin. J.* 1927, **56**, 73.
19. Stibbe, E. P. *J. Anat., Lond.* 1918, **52**, 257.
20. Urban, J. A. *Cancer*, 1959, **12**, 14.
21. Handley, R. S., Thackray, A. C. *Brit. med. J.* 1954, i, 61.
22. Margottini, M. *Acta Un. int. Cancer*, 1952, **8**, 176.
23. Wangensteen, O. H. *Ann. Surg.* 1950, **132**, 839.
24. Smithers, D. W., Rigby-Jones, P. *Acta radiol., Stockh.* 1959, suppl. 188, p. 235.

A KNIGHTHOOD in the Royal Victorian Order has been conferred on Mr. J. H. PEEL, who attended the Queen in her recent confinement. Mr. Peel is obstetric and gynæcological surgeon to King's College Hospital, director of clinical studies in the medical school, and a councillor of the Royal College of Obstetricians and Gynæcologists. To the many who know him in these and other capacities this honour will give particular pleasure.

Dr. VERNON HALL, who attended as anæsthetist, is appointed C.V.O. He joined the staff of King's College Hospital in 1931 and has been dean of the medical school since 1951.

INDEX TO THE LANCET

THE index and title-page to vol. II, 1959, which was completed with the issue of December 26, is enclosed with each copy of our present issue. This practice will be followed with future indexes; and accordingly those who wish to receive the index need no longer apply to our office.

Points of View

SOME UNCRITICISED ASSUMPTIONS IN PSYCHIATRIC THOUGHT

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IN current psychiatric thinking a number of unjustified assumptions are in constant use. As there is a growing tendency to train medical students and practitioners in psychiatric therapy—often very uncritically—an examination of some of these assumptions may be of value.

HOMŒOSTASIS

The concept of homœostasis is used in psychiatric theory in an unscientific way. Unfortunately, like so many other concepts in psychiatric theory, it has been borrowed from another science—in this case physiology. There it was introduced to describe mechanisms whose interactions maintain the constancy of certain physiological states—e.g., the respiratory mechanism, which maintains the tissue levels of oxygen and carbon-dioxide. It was realised that, for the cell to remain alive, its environment must be kept relatively constant, and that there must be many mechanisms serving this purpose.

Imagine, however, the harm that would have been done in physiology if no attempt had been made to uncover the complex interplay of reflexes and central nervous responses which explains the working of these mechanisms. Much painstaking laboratory work could have been saved by ascribing the activity of each of these mechanisms to an inherent homœostatic drive which came into play when any equilibrium was disturbed and returned it to normal. Thus, without any knowledge of the Hering-Breuer reflexes, the carotid body, and the respiratory centre, respiration could be attributed to the oxygen-seeking drive, or perhaps, for the more sophisticated physiologist, by the interaction of the oxygen-seeking and carbon-dioxide-avoidance drives.

Yet this apparently ludicrous state of affairs has been accepted widely in theories of behaviour. Just as it is obvious from the facts of cell life that homœostatic physiological mechanisms must exist, so for animal life to continue there must be similar behavioural mechanisms. For example, enough food and water must be regularly obtained, destructive stimuli avoided, sexual activity carried out, and young animals cared for. Hence a ready-made theory is available. Without further investigation of the mechanisms in the body which produce these activities, all this behaviour can be put down to a multiplicity of " homœostatic drives ", such as a hunger, a sexual, a maternal, and a pain-avoidance drive. Any other drive can be added as behaviour is observed which cannot be explained by those already in existence—such as the notorious exploratory drive, hastily invented when it was shown that rats learned the layout of a maze without being supplied with food, water, or any other incentive covered by a known drive. The valuable research which might have uncovered the physiological basis of this behaviour has been neglected; and instead the relative strength of these postulated drives has been measured and ad-hoc equations have been devised to fit the measurements.

This concept is also used in psychoanalytic theory as an explanation of behaviour which can be formally considered as tending to an equilibrium:

> " The assumption has been made in various forms by many biologists that there is a basic vital tendency [sic] to abolish tensions that have been brought about by external stimulation and to return to the energy state that was effective before the stimulation. The most fruitful conception in this respect is Cannon's formulation of the principle of ' homeostasis '. It was the same basic principle . . . for which Freud, following Barbara Low, often used the expression ' Nirvana principle ' . . . Homeostasis is, as a principle, at the root of all instinctual behaviour " (Fenichel 1946).

If psychiatry is going to borrow concepts from other sources, they must be used with the same accuracy. We know that homœostatic mechanisms must exist in behaviour, but we should study them to learn how they work, instead of using them to explain what they merely describe.

WE ALL HAVE DYNAMICS

The assumption that psychiatric illnesses can be explained in terms of " personality dynamics " is so well established that psychiatrists who find the knowledge of dynamics unhelpful in understanding and treating illness (the so-called organic psychiatrists) often reject the existence of dynamics in the healthy personality and in some personality deviations, or else use them with reluctance and embarrassment (Mayer-Gross, Slater, and Roth 1954). But surely it is the dynamic psychiatrist who should be embarrassed. Imagine the reaction of a physician to the following dilemma:

> He is told that his patient has just become ill; he is given the symptoms and a list of investigations of physiological mechanisms, but he finds there is no essential difference between the results of the investigations and similar ones on people without symptoms. Does he consider the possibility that these mechanisms are not responsible for the illness, that perhaps a new and as yet uninvestigated factor has caused the illness? No, he wastes no time with this easy and obvious solution: a new and revolutionary insight has come to him. All the people are sick, but only some have actually developed symptoms.

The dynamic psychiatrist seems to reach this position without recognising its illogicality. Having set out to treat the psychiatrically ill, he decides to investigate the processes in the sick and the healthy, showing in fact a preference for the healthy. This happened early in the development of dynamic therapy.

Freud's first book *Interpretation of Dreams* was not based on the study of symptoms—indeed not even on the study of patients. " I do not propose to make use of . . . the dreams of neuropaths, from which no valid inference could be made as to the dreams of normal people " (Freud 1953).

Next, when the dynamic psychiatrist discovered among the people without symptoms of illness a new group with a certain type of behaviour, he labelled the processes to which he attributed their behaviour as " neurotic ". This term showed not only that he assumed them to be pathological but also pathological in the same way as the processes in patients with neurotic symptoms:

> " thus the essence of normality is flexibility, in contrast to the freezing of behaviour into patterns of unalterability which characterise every manifestation of the neurotic process " (Kubie 1959).

This use of " neurotic " to cover two groups of people—those with symptoms of neurosis and those with a specific type of behaviour—is surely one of the most confusing assumptions of psychiatric thought. Admittedly there are people whose emotional behaviour is repetitive

and socially crippling: we have all met people with a long history of inability to accept instructions from people in authority; others who so need to be reassured of our regard that they test it by making greater and greater demands until they destroy it; and others whose behaviour varies consistently between complaisance and aggression. But is there any evidence that these people whom we all now describe as "neurotic" have any more symptoms of neurosis than the average "non-neurotic" (in this behavioural sense) members of society? At least we should stop to consider what relation, if any, exists between these people and those who have symptoms of one of the known psychiatric illnesses? The assumption of such a relation should not be allowed to go unquestioned merely because it has been masked by a change in definition.

Once he had attributed the behaviour in this group to a pathological—a "neurotic"—process, the dynamic psychiatrist went on to regard the processes in the healthy as pathological too. For the difference between the neurotic (as defined above) and the rest of us is only one of degree: we all have some need to reassure ourselves about other people's friendships and so on. By definition, however, it is not certain extreme forms of behaviour but the dynamics which produce them which are neurotic and so pathological. Hence we all have pathological dynamics: as Kubie (1959) puts it, "a neurotic process evolves in some degree in everyone". Note he does not say that the same dynamic processes which we see in the neurotic are present to some degree in everyone. The processes themselves are termed neurotic.

Superficially, organic psychiatry shows a similar tendency to treat some normal people as having underlying pathological processes—e.g., in the concept of the *formes frustes*. But there is a fundamental distinction. Let us take the obsessional personality as an example.

The organic psychiatrist would consider this a normal personality with valuable as well as harmful qualities. But, from the psychoanalytical viewpoint, the behavioural patterns of the obsessional personality are thought really to be concerned with fæces, to act as a defence against the emergence of pathological behaviour, and to indicate fixation at an anal level of development. The implication of pathology and of a somewhat crippled personality is unavoidable. Even the term "well-adjusted", often used of the approved personality, bears the clear implication there is something to adjust to.

Since the dynamic therapist sees the processes shared by the normal and the ill as pathological, it follows that he sees everyone as ill. So he abandons the definition of normal as "people without symptoms". Indeed Ernest Jones (1948) rejected the "statistically normal mind" and concluded that a "normal mind" in his sense does not exist.

Once everyone is ill, the presence or absence of symptoms is unimportant, and the dynamic therapist has rejected symptom-relief as an index of therapeutic success. In *Psychopathology of Everyday Life* Freud described the apparently meaningless random acts which everyone carries out as "symptomatic acts", thus making (and masking) the fundamental assumption that they are comparable with psychoneurotic symptoms. Once aspects of normal behaviour—initially errors and dreams but later patterns of emotional behaviour—are treated as identical with symptoms, symptoms themselves can have no significance.

This lack of interest in symptoms is only part of a general attitude towards all overt behaviour. As the dynamic therapist is concerned only with the processes within the patient, what actually happens to the patient is of little importance. This attitude explains why the dynamic therapist, having actually described the characteristics of overt behaviour in the neurotic, has made no effort to distinguish them from the normal. To do so he would have to assess the degree to which this type of behaviour was present—that is, he would have to make a social judgment as to how the patient is managing his relationships with his friends, at his work, in his sexual activities, and so on. The therapist, by virtue of his method of never seeking information, is unable to obtain this material, and in any case he does not regard statistical normality in these respects as evidence of mental health. Often analysts seem to prefer, as patients, people without overt evidence of illness: after all their dynamics are the same, and there are no troublesome symptoms to occupy the patient's attention and get in the way of therapy. This is seen in the hospital or clinic where the analyst becomes more interested in the staff than in the patients.

It would seem that really the dynamic psychiatrist has always been interested in the motivations of the normal, but has excused and masked this interest by adopting a new set of terms which enable him to see the normal as pathological and indeed as no different from the patient with a neurosis. But in fact there are two continuums—the normal and the psychiatrically ill and the normal and the neurotic. Though the distinction in both cases is one of degree, it is no less real than the distinction, say, between short and tall.

Accepting that these two continuums exist, we could agree that the dynamics revealed in the normal and the neurotic often seem helpful in understanding the behaviour of these two groups. Awareness of the dynamics may be useful in treating the neurotic, provided some sense of proportion is maintained about what behaviour actually justifies treatment. But are they of value in the understanding and treatment of psychiatric illness? Often the dynamics revealed in the psychiatrically ill are just as apparent once the patient has recovered. Again similar dynamics seem to be described in different psychiatric or even psychosomatic illnesses as well as in apparently healthy people: thus guilt about the expression of hostility is recognised in anxiety states, obsessional neuroses, depression, migraine, and hypertension—not to mention its presence in many of the colleagues of the dynamically orientated. Are these dynamics necessarily related to the illness or are they basic to the normal-neurotic continuum of personality present in everyone sick or well?

Possibly emotional factors are responsible for the onset of a psychiatric illness; but could they not be so in the manner that a lowering of resistance is responsible for the onset of an infection? Once the infective process has begun, its symptoms and treatment must be understood in terms of the attack of the specific organism on the body, not in terms of the processes causing the lowering of resistance. Could not a disturbance of the patient's dynamics allow other factors to produce the illness? Another possibility is that the psychiatric illness, once present, will be used by the patient for his own emotional needs, thus producing an apparent dynamic reason for the illness.

At least these possibilities should be considered, especially when there is growing evidence that the dynamic treatment of psychiatric illness has no more success than would be expected from spontaneous

remission (Schmideberg 1958, Hastings 1958, Wallace and Whyte 1959). Certainly this evidence is not entirely convincing: since the relief of symptoms is never used as a criterion for the success of dynamic therapy, no completely valid measurement of its value will ever be possible. But could not this be evidence of the analyst's recognition (dare we say unconscious?) that his therapy is suited to the readjustment of personality dynamics rather than the relief of symptoms. And in fact may not this be the rightful place for this treatment? People sometimes come to the psychiatrist, not with an illness, but with a personality they wish changed. The psychiatrist who is unsympathetic towards a dynamic approach may not be interested in such a patient. Surely if this person is really motivated to change, if he is prepared to be interested in the unravelling of his dynamics, and if he is verbally intelligent enough to understand the concepts that would be used, he may be helped by dynamic psychotherapy.

THE AGGRESSIVE *v.* THE NON-DIRECTIVE PSYCHIATRIST

There is an increasing belief that general practitioners should be trained in dynamic psychotherapeutic methods, and courses have been started in some centres. But the propagation of psychiatric theory without sufficient awareness of its implicit assumptions has in the past proved harmful. For example, theories which laid stress on the damage done to the personality by incidents in childhood, without at the same time emphasising the creative positive role of environment, led to the idea that any influence might harm the child and hence to the concept of a completely " permissive " upbringing.

Now the danger exists that a potentially harmful form of treatment will become available to those who will be aware only of the damage that can be done by alternative methods of therapy. For many years the psychiatrist who uses physical methods has been reproached by his dynamically oriented colleague for expressing his own aggression in these methods. Again, " directive psychotherapy "—that is to say, actually giving the patient directions about how to manage his problems—is regarded as unrefined and brutal. The implication is that the dynamic method of treatment is infinitely more gentle. But let us examine this method, in its pure form.

The patient goes with an illness to his dynamically oriented doctor to find that at the end of his consultation, even though he may have specifically asked for this information, he has not been told what is the matter with him, how long he will be ill, what treatment (if any) he will receive, or even whether he will recover or not. However the doctor has listened carefully and given him another appointment. As the consultations grow in number and the patient asks more persistently for reassurance on these points, he is still denied it. Nevertheless the doctor shows a regard for the patient by continuing to grant regular and long interviews. The patient must surely feel extremely anxious and annoyed with his doctor for denying him what he is so used to expecting in the usual doctor-patient relationship. Yet he must also feel grateful to the doctor for the unique degree of interest shown.

Further evidence of this interest is the doctor's regular " interpretations " of the patient's behaviour. But the patient must also regard these interpretations as indicating behaviour on his part which falls short of the ideal, and which should be changed: that is to say, he must regard them as being both criticisms and directions. Many analysts seem to believe that in their interpretations they reveal the truth to the patient in a completely objective fashion. This may be so, but if the purpose of the treatment is to change the patient, the interpretation must be the most important means. And surely the patient is aware, or at least expects, that he is to be changed by treatment, and soon realises that the main treatment he receives is by the interpretations. Hence he must take them as indications to change and as criticisms that his present behaviour is less than ideal in these respects. And given the dynamic therapist's view that the healthy mind does not exist, there will be no shortage of areas where the patient's behaviour is not ideal.

Of course no matter how objective and valid the interpretations are, many must be felt by the patient as critical—e.g., when he is told he is seeking the love, sympathy, or approval of the doctor, or when he asks for treatment and is told he is seeking a magical solution to his problems. However, apart from this, I believe that interpretations which are not overtly critical and directive must be felt as such when given in the therapeutic situation—i.e., when the patient is expecting treatment which will change him.

So the patient must feel he is both denied reassurance and continually criticised; for he is always being told where his behaviour falls short of the ideal, without ever receiving any praise for his positive qualities. At the same time the therapist delivers these intellectual criticisms in a completely objective manner, without any sign of emotional disapproval, and in fact gives the patient signs of approval, albeit unemotional ones, in that he continues to give regular and long interviews in which he shows great interest in the patient. In short, in this situation the patient must, and does, develop ambivalent feelings of resentment and gratitude to the doctor—the " transference feelings ". To make these feelings more certain and intense the interpretations are useful again. For whether the patient speaks of his love for his wife, his jealousy of his siblings, his need for the regard of his employer—indeed whatever he talks about—he is told he is really talking about his feelings to the doctor.

The patient is unable to express much of the resentment he feels in the interview. He is prevented partly by his feelings of gratitude and obligation, perhaps also of respect towards the doctor, but probably mainly because his resentment seems irrational and unfair in face of the doctor's apparent objectivity and lack of emotion. So the patient departs from the interview annoyed and takes out his anger on his workmates, relatives, or friends. The damage the patient can do in this way is accepted by the dynamic therapist, who calls it " acting out ".

In brief, a situation is constructed in which the ill patient is held by feelings of obligation and hopes of recovery, and must tolerate not only a complete lack of reassurance but also continued intellectual criticism from a doctor towards whom he is encouraged to develop extreme ambivalent feelings. At the same time he is denied any help in dealing with his immediate problems, many of which may be due to the acting out of these feelings. This same doctor regards as overtly aggressive a colleague who tries to help the patient to deal with his symptoms and his problems. But is not the dynamic situation one of the most subtle and refined means of expressing passive aggression devised? May not this personality characteristic influence the psychiatrist in his choice of therapy, and does this tendency to passivity explain his choice of the word " non-directive " to describe this treatment. His apparent unawareness that the development of an intense emotional yet ambivalent relationship is a powerful manipulative process—possibly the most powerful known to man—seems otherwise inexplicable. It would show a clearer understanding of this technique if it were described as " non-supportive " rather than " non-directive ".

Dynamic psychiatrists who work with schizophrenics seem to recognise that the technique is extremely traumatic to and demanding of the patient.

> " Abandon analysis of the positive transference; negative transference, of course, may come of itself, and must be overcome by explanation, psychoanalysis and the analyst's

behaviour. . . . The psychiatrist must preserve the positive transference by siding with the patient in any of his conflicts " (Federn 1953).

" Too much is expected from the psychiatric patient as a rule: a degree of co-operation, insight, and will-power we would not demand from a physically ill patient, yet the psychiatric patient is (by definition) much more disturbed " (Schmideberg 1958).

What advantages has it to compensate for these disadvantages? It is possibly the most satisfactory method of revealing dynamics.

Obviously the patient's description of his own feelings and behavioural patterns cannot be accepted because of his lack of insight and resistance to accepting the truth about himself. A relative or friend's description may also be biased. Both lack sophistication in understanding and describing behavioural patterns. Only by actually experiencing the emotional demands the patient will make of a person who is important to him and by actually seeing how he expressed his feelings of love and aggression, can a psychiatrist fully appreciate the dynamics of a patient's inter-personal relations.

If we accept that " non-supportive " psychotherapy, though illuminating to the doctor, is disturbing to the patient, should we not choose carefully the type of patient with whom it should be employed? Surely patients who come to the psychiatrist for the relief of an illness should not be denied the support and reassurance of the normal doctor-patient relationship? The decision to deny the patient this support should be taken only when there is good evidence that the patient can tolerate this, is eager to have his dynamic patterns changed, and is able to understand the abstract verbal concepts which will be used by the psychiatrist to give him insight.

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Special Articles

STAPHYLOCOCCAL INFECTION IN NURSES

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IN recent years the serious and worsening problem of staphylococcal infection in hospital has had close attention. But this has been directed mainly to cross-infection in surgical wards, epidemics among the newborn, and pneumonic superinfection in patients with influenza. One important aspect has been comparatively neglected —namely, the high incidence of minor staphylococcal infections among nurses and the considerable amount of working time lost thereby.

INVESTIGATION

In the twelve months ended last June at The London Hospital, a record was made of the number of staphylococcal infections occurring in nurses, the sites of these infections, and the time the nurses were off duty because of them. In addition, in 100 cases the sensitivity of the infecting staphylococcus to four antibiotics was studied and compared with the findings in an equal number of inpatients and outpatients during part of the same period.

RESULTS

Among approximately 725 nurses on duty at the main hospital there were 146 cases of staphylococcal infection. This figure represented 16·4% of the total admissions to the nurses' sick-quarters. (In the previous six years the proportion had averaged 18·2%.) The working time lost by the affected nurses was 1249 days, an average of 8·5 days each.

TABLE I—DISTRIBUTION OF LESIONS IN 146 CASES OF STAPHYLOCOCCAL INFECTION IN NURSES*

Site	Face	Nose	Ear	Eye	Neck	Axilla	Arm	Hand	Fingers	Trunk	Pubis, perineum, buttock	Thigh, leg	Foot, toes
Number	21	6	7	22	4	12	8	1	43	10	5	6	5
Totals	60					64				15		11	

* The total amounts to more than 146 because some nurses had lesions in more than one site at the same time.

TABLE II—ANTIBIOTIC SENSITIVITIES OF STAPHYLOCOCCI ISOLATED FROM NURSES, INPATIENTS, AND OUTPATIENTS

—	Number	Percentage of staphylococci resistant to:			
		Penicillin	Chloramphenicol	Tetracycline	Erythromycin
Outpatients	100	75	1	10	..
Inpatients	100	88	4	50	..
Nurses	100	98	4	35	1

All the infections were of skin or soft tissues. (A case of staphylococcal pneumonia complicating influenza was excluded from the series.) As table I shows, the commonest site of infection was the finger (29%), and 83% of all lesions were on the face, neck, axilla, or upper limb.

When the sensitivity of the staphylococci was tested, almost all (98%) proved to be resistant to penicillin, about a third (33%) to tetracycline, just a few (4%) to chloramphenicol, and only 1 to erythromycin (this organism being sensitive to chloramphenicol, oleandomycin, and novobiocin). Table II shows (1) that penicillin-resistant strains were more often found in the nurses than in the comparable series of outpatients and inpatients; (2) that tetracycline-resistant strains were commoner in the nurses than in outpatients but not quite so common as in inpatients; and (3) that the proportion of chloramphenicol-resistant strains was small and equal in nurses and inpatients, and even smaller in outpatients (though the difference is probably not significant). Erythromycin sensitivity was tested in too few patients to allow useful comparison.

DISCUSSION

In nurses staphylococcal infections have a nuisance value out of all proportion to their severity; for, even when a lesion is trivial, the nurse must be removed from contact with patients until it has healed completely. In most other occupations (except food-handlers and certain pharmaceutical workers) less working time need be lost.

The proportion of nurses staphylococci resistant to the four antibiotics mentioned roughly reflects the frequency with which these antibiotics are used at The London and most other British hospitals. (In our nurses' sick-quarters antibiotics are used as little as possible, and

chloramphenicol and erythromycin are reserved for very serious infections—fortunately rare—resistant to penicillin and tetracycline.)

The distribution of the lesions suggests that the most important factor in infection is direct skin contact. This raises the practical question whether repeated use of a hand scrubbing-brush during working hours may play a part in the high incidence of finger infections, and whether the incidence could be lowered by discontinuing the use of such brushes. Though no definite conclusion of this kind can be drawn from the present investigation, it is obvious that staphylococcal infection in nurses deserves further study, particularly since many chronically understaffed hospitals cannot afford the loss of working time which it causes.

I am grateful to Lord Evans and Mr. J. E. Richardson for permission to publish this paper and to Dr. H. B. May, director of the clinical laboratories, for helpful advice and for permission to quote the results of routine antibiotic sensitivity tests carried out by his staff.

NEW HOSPITALS IN ULSTER

IN the five years since 1954, capital expenditure on hospital and specialist services in Northern Ireland has amounted to £7 5*s*. per head of population. In the rest of the United Kingdom capital expenditure in the five years has been £1 14*s*. in England, £2 16*s*. in Scotland, and £2 6*s*. in Wales. The Northern Ireland Hospitals Authority has spent about £15 million on capital development since it took charge of the hospital services in 1948, and it is now spending about £3 million a year. One reason why the Authority has had opportunities that have been and are the envy of regional boards and boards of governors elsewhere is that Northern Ireland had tremendous leeway to make up in hospital building; and excuses for economy and delay that could be made to sound reasonable in England, Scotland, and Wales in 1948 (and in 1960) were totally unconvincing in Ulster. Moreover, labour and materials have been easier to find in Northern Ireland since the war than in many parts of the United Kingdom; and, given the money, the Hospitals Authority was able to avoid some of the frustrations of shortages and get on with several ambitious plans. Thus the Authority is now in the fortunate position of being responsible (among many other new things) for the first completely new general hospital to be built in the United Kingdom since the war (the North West Hospital, at Altnagelvin, near Londonderry), the first mental hospital to be built in the United Kingdom since the war (the Gransha Hospital, also near Londonderry), and the first substantial institution to be built in Northern Ireland providing inpatient care and training for those suffering from incomplete or arrested development of the mind (the Special Care Service Hospital at Muckamore Abbey, near Antrim).

Altnagelvin

The North West Hospital stands on high ground a mile and a half from the centre of Londonderry, and most of the wards in the 150-feet high building have wide views to the south-east over the impressive country around the Pass of Glenshane. Work began on the site in 1951 and the hospital came into use on Feb. 1 this year. Its cost is about £2,600,000.

The main building, set in 50 acres, has twelve floors, including basement, in the ward wing, and eight floors in the treatment wing, the two wings forming an L. At present there are 394 beds, but at a later stage the L will be converted into a T containing in all 550–600 beds. There is also an outpatients wing, attached to the main building, and separate buildings for mortuary, laundry (designed to serve a number of local hospitals), main kitchen, and garages, boiler house, and workshops. The staff is housed in a nurses' home for 193 nurses, matron's bungalow, doctors' hostel, and engineers' house.

Within the main building, visitors move separately from hospital traffic until they reach their respective wards. They use the three bed lifts arranged with doors at opposite sides so that access to the "hospital" corridor is separate from access to the visitors' waiting-spaces.

The four main theatres and a plaster room are on the seventh floor of the treatment wing, and a small emergency theatre and X-ray room are placed near the ambulance entrance. In the ward wing a typical unit consists of one 6-bed, five 4-bed, and five 1-bed wards.

The external facings on the main building are largely precast concrete units, using exposed aggregates from local sources, and brickwork described as "buff-orange". The entrance to the hospital is presided over by a striking bronze figure (by F. E. McWilliam) of Princess Macha, who is reputed to have founded the first hospital in Ireland.

The hospital replaces three small hospitals in Londonderry, one of which, the Londonderry City and County Hospital, is to be adapted for use as a special unit for sick old people.

Architects: F. R. S. Yorke, E. Rosenberg, C. S. Mardall; associate architect, J. R. B. S.-Penoyre; architects in charge, W. G. Lucas, A. R. Parry. In association with H. W. Scatchard, architect to the Northern Ireland Hospitals Authority.

Gransha

This £2 million mental hospital in the villa style is being built near Londonderry and the shores of Lough Foyle on a site acquired by the previous governing body of the hospital sixty years ago but hitherto little developed. The first building contract, now completed, provided villas for 90 patients, an admission unit for 60 patients, and a convalescent unit for 28 patients. The present contract will supply three more villas (180 patients), an administration block, and patients' recreation halls. Further contracts are expected to expand the hospital to 750 beds. Accommodation is supplemented by the site's original buildings (185 beds), which are to be modernised. The first plan was to have 30–40 patients in each villa, but it was later decided to build each villa for 60 patients, arranging the accommodation so that a villa could be used if necessary as two self-contained units of 30 beds each.

The 150-ft. high 11-storey ward wing of the North West Hospital, Altnagelvin, Londonderry, facing south-east to the Pass of Glenshane.

Patients may be retained for several months in the central admission unit if the prospects of early return to the community are encouraging. Of the three villas for men at present in use, one is open and run by the patients themselves, another is open and supervised by a nurse, and the third is partly closed and supervised.

Architects: J. M. Sheppard & Partners, London.

Muckamore Abbey

Another £2 million has been devoted to this establishment for special-care (mentally defective) patients. Before 1948 there were no special colonies or institutions in Northern Ireland for persons requiring special care, and the only accommodation outside patients' homes was in mental hospitals. Muckamore Abbey is the first specially constructed colony in Northern Ireland. The Muckamore estate of 192 acres was acquired in 1949, and some female patients have since been accommodated in the existing house and in aluminium prefabricated buildings nearby. 154 more acres were acquired in 1951.

The patients are housed in villas each taking 40 or 50 patients. The male and female sites are divided by administration buildings, recreation hall, and school of nursing. There are separate workshops for male and female patients. The sick hospital of 70 beds will have 40 beds for general patients, 20 for tuberculous patients, and 10 isolation beds. A school for 350 children is to be built.

The prefabricated buildings are now being used for children, and when permanent quarters are ready for them the aluminium buildings will be used for old patients and young infirm patients in need of special care.

The aim is to provide a sheltered community, with very little restraint, where the handicapped can feel at home and useful, and to prepare them, if possible, for a return to the outside world.

Architects: J. M. Sheppard & Partners, London; Ostick & Williams, Belfast.

Geriatrics and Surgery

Wakehurst House,* the first unit of its kind designed and built in the United Kingdom for the rehabilitation of elderly invalids, is connected to the existing geriatric unit at Belfast City Hospital. The new building accommodates 40 men and 40 women in large open wards partitioned to give small units of 6 or 4 beds. A 16-bed wing on each of the two ward floors forms a self-contained long-stay unit, so that each ward sister has 40% of long-stay invalids, with the necessary staff to look after them and the other 24 patients undergoing rehabilitation. The 24-bed rehabilitation section includes a large exercise bay which gives more room for physical retraining than is found in the usual ward layout.

Nuffield House is an experimental theatre block which was opened in October, 1957, at Musgrave Park Hospital, Belfast. The plans were prepared as part of the Nuffield Provincial Hospitals Trust's Investigation into the Functions and Design of Hospitals. The completion of the building was the responsibility of the research body which succeeded the Investigation—the Division for Architectural Studies, which is part of the Nuffield Foundation The unit contains 80 beds with operating-theatres, X-ray facilities, and a central sterile supply department. This department meets the whole demand for sterile goods used in treating patients in the hospital's 700 beds, and also supplies the operating-theatres with all sterile goods except surgical instruments. The equipping and running of the department have been closely studied and analysed, and modifications introduced from time to time.

This attractive building, which makes the adjoining temporary hospital huts of the late war look very temporary indeed, is really the first stage in a major scheme of reconstruction at Musgrave Park. The wartime buildings will go, and eventually the hospital will be almost entirely new.

This is only part of the building and reconstruction that has been completed or is in hand to improve the Health Service in Northern Ireland—from local-authority clinics to the £2,500,000 Ulster Hospital now building in Belfast. New acute hospitals will also be provided at Enniskillen, Coleraine, and Dungannon; and at the main teaching hospital centre (the Grosvenor Road site, Belfast) there will be a suite of new operating-theatres, a new eye, ear, nose, and throat hospital, an extension to the Royal Belfast Hospital for Sick Children, a new out-patient department, and a new dental hospital—at least £3 million of improvements.

* We hope to publish soon an article by Dr. G. F. Adams, physician in charge of Wakehurst House, about the design and purpose of a hospital geriatric unit.

THE AMERICAN VERSION OF THE WELFARE STATE

SINCE the great depression of the '30s precipitated the Social Security Act of 1935, welfare schemes in the United States have grown rapidly; but Mrs. Dorothy Wilson's illuminating survey [1] shows that the American citizen is not offered the same help and support as in this country. In a Federation of equal States, where private enterprise and dislike of Government enterprise are strong, it is not surprising that the schemes should be complex and uneven. Much more is done than might be supposed from some American comments on the British system, but there are some sizable gaps.

Pensions

Under the Social Security Act of 1935 and its amendments of 1939, 1956, and 1958, Federal schemes provide old-age, survivors', and disability pensions which cover 90% of the gainfully occupied population (self-employed doctors being one of the principal groups excluded). The old-age pension scheme is completely self-financing: employer and worker each pay a tax of 2½% on the worker's earnings. Pensions are related to earnings, and range from about a third of earnings at the maximum level to about half at the lower end of the scale. Survivors' and disability pensions are also related to earnings.

Disability and Unemployment Allowances

A totally disabled worker becomes entitled to a pension at 50. Under that age he may be eligible for "compensation payments" or sickness benefit for a limited period, after which he will have to seek public assistance. Compensation for industrial injury covers less than four-fifths of the working population. Employers must supply medical aid to the injured, but in some States the amount of medical attention and the length of time for which it is given are limited.

The duration and size of unemployment benefits also vary from State to State.

Public Assistance

Public assistance is administered by each State and is much more selective than in Britain. Towards benefits for special categories—such as the aged, the blind, and the totally disabled—the State receives a Federal grant, but outside these categories assistance is the responsibility of the State Government. For the medical-care of people on public assistance the Federal Government matches payments made by States and local authorities. Because of the absence of any national health-insurance scheme and the rising cost of medical care, more and more people are turning to public assistance when they are ill, and in 1957 about a tenth of the total expenditure on public assistance consisted of payments for medical care.

Since there are neither Federal funds nor supervision for general assistance, the standard varies greatly. In some places it is the same as for people in the special categories, in others it hardly exists. Thus, in a country with exceptionally high standards of living it is yet possible to be really destitute.

Sickness Benefits

There is no national system of sickness benefits, though rather more than half the workers are covered by schemes

1. America and the Welfare State. *Planning*, 1960, **26**, no. 439. (Published by P.E.P., 16, Queen Anne's Gate, London, S.W.1, at 5*s*.)

arranged on the initiative of employers, trade unions, and some State Governments. The payments made are usually 50–60% of the wages, but for a limited period.

Health Service

The Federal and State Governments provide medical care for certain groups of people and for certain diseases, either by payments to private hospitals and doctors or in public hospitals. In 1958 some 30 million people (about a fifth of the population) received medical care in these ways. About 23 million of them were Veterans or their dependants. This specially favoured group have their own hospitals. In 1958 almost a quarter of the total expenditure on medical care came from public funds.

The ordinary citizen receives no Government help in time of illness. Medical costs are high, and nearly three-quarters of the population cover themselves by some form of private hospital insurance. But this leaves nearly 50 million people with none. In 1958 the sums paid out under health-insurance policies covered only about a quarter of the nation's sickness bill.

COMPARATIVE COSTS

The United States social-security services absorb 8% of the nation's personal income, ours 11%. We spend large sums on family allowances, have more retired pensioners, and draw more of our expenditure on health from public money (90%, compared with 25% in the U.S.A.).

In both countries retirement pensions were the heaviest item in the social-insurance budget. In the United Kingdom they claimed two-thirds of the social-insurance account, in the U.S.A. a half. In the U.S.A. a single group, the Veterans, received 16% of all social expenditure, compared with 5% spent on war pensions in the British budget. Admittedly our war pensioners received further concealed help through other services, such as the N.H.S.

The U.S.A. spent $22,000 million on health and medical care in 1957–58, but only about a quarter of this sum came from public money. 20% came from private health-insurance schemes, and over half direct from the citizen's pocket, representing about 3% of his personal income. In our country in the same year £660 million was spent on the N.H.S. The direct cost to the citizen was his weekly contribution of 2*s.* 4½*d.* and £27 million for N.H.S. charges for prescriptions, dentistry, glasses, and so on. In this country people are still paying considerable sums on private medical care—probably about a tenth of the total health bill.

SOME CONCLUSIONS

From her survey Mrs. Wilson concludes that in both countries the lower-income groups probably owe more of their improved living standards to full employment and higher output than to the Welfare State. The British State offers more comprehensive cover and as a result has spread its benefits more thinly. Many people are being helped who could afford to help themselves, while others are not getting all the help they need. As a result of this policy, capital expenditure in the health service has been severely restricted and there has been little left over for research.

Our benefit schemes fall into the same pattern. Nobody is left absolutely destitute, as can happen in the United States. But our flat-rate benefit of 50*s.* a week is inadequate for post-war needs, and in 1958 one in five of all households receiving retirement or unemployment benefits had to seek National Assistance.

On the whole Mrs. Wilson finds that the U.S.A. benefits do more than the British benefits to replace the income of those they help, but they are not comprehensive either for those they help or for the circumstances in which they give help. She regards this as a serious flaw in the American version of the Welfare State.

In England Now

A Running Commentary by Peripatetic Correspondents

AT my alma mater, the subject of rugby was carefully avoided. Only once did I venture as far as a first-round match, happily drawn against the only other side in London with an equal lack of talent. The winner was to meet the victor of Guy's *v.* Mary's, and it soon became painfully obvious that this was an honour both sides were anxious to forego. However, it must be conceded that the match was a masterly exhibition of how not to score any points, and even after two replays the score stood at a resolute draw of 0—0. Unfortunately, at the third replay, in one of the abundant free kicks which characterised this series, someone on our side (possibly distracted by the vociferous exertions of a small band of female students) inadvertently kicked the ball over the bar. Thereafter, the score stood firmly at 3—0. The subsequent encounter with Guy's, when the score was somewhat unnecessarily 98—0, realised our worst fears.

However a new allegiance has changed my attitude, and last Wednesday I not only watched my hospital play in the Cup Final but saw it bring off a resounding victory. The preliminaries to the match were elaborate. A band paced the pitch in splendid style and the loud cheer greeting the request for non-players to leave the field was no reflection on their performance, which was at once manly and stirring, though at no time could any tune be actually discerned. The far end of the field was dominated by a heavily armoured green-grocer's cart which successfully repulsed the most determined assaults with a hail of decomposing merchandise.

Since the victors had many moments of fine play and superiority, loud expressions of parochial pride came without difficulty, punctuated as they were by violent explosions from a heavy cannon mounted at the far end of the field on a vehicle which had clearly seen better days. From the vehemence of your correspondent's endorsements of such cries as " Kill the b——s! ", few would have guessed that they sprang from loyalty by adoption.

* * *

Some time ago [1] I described in affecting terms—at least they affected me—how the path through Blossom Wood had become overgrown because Ted had got a motor-bike and no longer walked along it to his work. Now it is back again—even more so—and again the cause is the internal combustion engine.

Reablement was phased, as we say when we haven't got enough money to rebuild a hospital all at once. Stage I was heralded by what sounded like a machine-gun battle in the wood, and the following Sunday the lane was blocked by scores of cars and motor-cycles whose occupants had come to watch—and incidentally break down my hedge—a motor-cycle " scramble " with 150 entrants from all over the country. The riders went down a wet ditch, along a stream, through a swamp, and then up an almost vertical muddy slope which, though allowed to do almost anything except carry their bikes on their shoulders, not one of them succeeded in climbing. Quite incidentally they drove along the old path through the wood and opened it up again.

Stage II started with the arrival of a pile of logs with curious orange centres, where the path enters Blossom Wood from the lane. Reconnaissance showed them to be alder logs from the banks of the stream in the field beyond. They had been hauled on a tractor through the wood, and the path was now a broad, and unusable, mud-track. My spies tell me the logs are awaiting transport to a manufacturer of toys down Chichester way. Alder wood has not many uses now that clogs are no longer fashionable in the North, and why should a toy-maker want it? The answer—no splinters.

* * *

It must be nice to have one's name attached to a disease which one has discovered, and in the past those who like to collect rare conditions and to publish accounts of a case or three had grounds for hoping that such an honour would come their way. Now Asher has shown us that this will not

1. *Lancet*, 1958, ii, 521.

happen unless we are possessed of an extraordinary moniker. Having an utterly unmemorable name I have given up the struggle. Instead of inventing diseases to go with my name I have turned to inventing names to go with the diseases. This is a good thing because in our area the professor is very keen on classification and has provided us with a modification of the *Nomenclature of Diseases* which covers every eventuality, he hopes. However we are always adding to it. When I sent in "Queer-shaped nut" for a child whose head was not exactly plagiocephalic but nevertheless out of the true, I was rebuked for levity. I am now deadly serious, and here is the result.

I often see children who are fit and well but who are considered by their parents to be diseased because they have been comparing them with other children in the family for so-called lateness in talking, thinness, fatness, and so on. Well now: *dys*—difficulty, *confero*—by comparison, *sibl*—with a sibling, *osis*—osis. *Dysconferosiblosis*, easy. There is an even more serious disorder in which it is the neighbours' children who are used as the yardstick. This is covered by the designation *Dysconferojoneses*. I thought that perhaps that was the end, but only yesterday I came across a worse case. The child, a late talker, was being compared with not only his elder sister, who started to talk early and has never stopped, but also with his younger brother, who is grosser, and with the neighbours' brat who can sing and play the piano, and is obviously headed for the top ten. There is only one thing for it I am afraid: *Dysconferojonescumsiblosis*. In Polish, and more neatly, *Dyskjksosis*.

Apart from this I often see children whose psychological troubles seem to stem from the fact that one or both parents are foreigners. The child has to come to terms with two languages at the same time, and while the more brilliant ones can do it easily the duller ones become confused and may show various behaviour disorders. No *osis* here, let's just call it the Tower of Babel syndrome.

* * *

If formal dining out is the socially accepted method of suicide for elderly gentlemen, then the cocktail party must be a close second. Talking blah in an upright position for ninety minutes does nothing for the spine, and only 'Breathalyzer' tests for all motorists after 7 P.M. will save us. The dinners seem to consist of stuffing food into stomachs already suffering from too much for too long. What a good thing it would be if we swopped with a teen-age rock-an'-roll outfit. They could have the seven courses and we could have the milk and sandwiches. A creaky session of R. and R. for afters might not be elegant but it would be good for the figure.

* * *

From the point of view of the reporter sent by the local weekly newspaper it was a more than usually dull meeting of the executive council. Not a single doctor anonymously reprimanded; only one dentist fined a trifling matter of £4. Nothing meaty at all. The whole afternoon was spent on the need—long established but still unfulfilled—for a pædiatrician in the area. A full account of what had been said by the H.M.C. to the R.H.B., and of the comments of the L.M.C. on the R.H.B.'s reply—a bewildering collection of letters and initials, all about a pædiatrician, as yet non-existent . . . Back to his office went the reporter to write his account of the meeting. What would attract the reader's eye to such a dreary subject? What simple phrase would carry the required punch? At last he found it. Printed in splendidly arresting heavy type his headline ran: CARE OF COUNTY FEET—CONSULTANT SERVICE ASKED FOR.

* * *

INFORMATION PLEASE

To be, or not to be; that is the question—
And since 'tis equiprobable, the choice
Requires but one small Bit of Information.
Whether to live—eat, drink, and sleep
(Though in that sleep what dreams may come)
Or die, and dying write another name
Among the actuarial statistics. Ay,
The little more and yet how much it is;
It needs one Bit—the Bit I do not have.

Letters to the Editor

THEATRE STAFF

SIR,—The patient's limbs slipping off the table because the staff do not know how to fix them in position, the diathermy that does not work because it has not been plugged in to the wall, the abdomen reopened at the end of a long operation because someone has taken a swab outside in a bucket—how well we know and how sick we are of this sorry tale of incident and accident that punctuate the progress of our operating-lists. I have had a junior nurse fill up the cystoscopy cistern with boiling water from the steriliser. I have asked a nurse to shut the door only to discover that she did not know enough English to understand what I meant. I am regularly stopping to show nurses how to tie on a gown, and giving them the warnings without which a casual spectator would not be allowed into the operating-theatre. Surely this is not necessary. "Oh, but our nurses must get their training. The General Nursing Council . . ." But trained for what? Not one of these girls will ever put her nose inside a theatre again once she leaves her training-school. Why train them for a task they will never be called on to undertake?

By all means let the Dean of the Institute of Basic Medical Sciences (March 12, p. 604) do something about it if he can, but I doubt whether he will succeed: the opposition is too well entrenched. And why does he start by appealing to the Ministry? This is a matter for internal decisions in the first place, but I suppose that means raising it in committee, which is the surest method of shelving the whole business for another decade or so.

London, W.1. STEPHEN POWER.

ANTI-SMOKING CAMPAIGN

SIR,—Whilst agreeing with the authors of the paper (Feb. 6) on the Efficacy of an Anti-Smoking Campaign that the status of health education is not high enough, I feel that the lack of success achieved as a result of their considerable efforts in their campaign may be due to the very reasons mentioned in their preamble. It is unfortunate that before embarking upon such a vast and costly enterprise, so little attention was paid to the scientific evidence already accumulated on the conduct of health-education programmes and the use of audiovisual media in this field.

The main object of health-education activities is the alteration of individual and community attitudes leading to changes in patterns of behaviour conducive to positive health. It is now well known from studies, both at home and abroad, that this end is best achieved when the educationalist uses a personal and socratic approach rather than impersonal and didactic methods and media. The latter are useful for stage-setting and the creation of interest in specific topics, particularly in the field of environmental health. They do little to create the feeling of *total personal involvement* in matters of individual health and wellbeing. This is especially true when the recipient of the didactic approach has been the subject of considerable propaganda bombardment over a long period of time from the opposing viewpoints. Under these circumstances attitude and habit changes are rarely brought about by the academic and intellectual revelations associated with didactic methods (witness the still large number of the profession who continue to smoke). Personal conviction develops as a result of ingestion and incubation of facts followed by social rumination, particularly when this takes place under specially created and controlled circumstances. Opportunities for these social exchanges should be provided in the course of any campaign by using such methods

as the group and arena discussion, individual and group interviews, and open forums. These are known to be extremely effective in creating within the individual the sense of personal involvement leading to the alteration of attitude and behaviour patterns. Such organisations as the Central Council for Health Education have accumulated considerable evidence in favour of the use of these methods. In the campaign described considerable use was made of mass publicity media and didactic methods. No mention was made of the use of these personal and socratic techniques, nor does it appear that consideration has been given to the possibility of a follow-up campaign, in which they would be used.

A social health problem of this magnitude demands continuous personal rather than financial effort and one in which all who have a responsibility in the wellbeing and care of the community as part of their day-to-day duties should be involved. In addition to the doctors, there are health visitors, district nurses, public-health inspectors, &c., who have a considerable part to play and can make a very definite contribution, at their own level of professional activity. It was indeed unfortunate that no programme of in-service training for these groups appeared as part of the campaign planning.

The negative findings of this project are of great value because they demonstrate the ineffectiveness of this type of impersonal campaign. They also show that the media used were unsuitable, thus underlining the need for proper pretesting and evaluation. It would be of interest to know whether low-intensity work, using the personal methods described, is contemplated and whether in the long run this will have a greater and more lasting effect on the recipients of the original campaign.

Sheffield. F. ST. D. ROWNTREE.

PLACENTA PRÆVIA

SIR,—It is indeed difficult to follow Professor Macafee's argument (Feb. 27) against radiological investigation in cases of placenta prævia, and since he has mentioned my name I take issue with him.

He begins by stating that "it is in cases of antepartum hæmorrhage at 30–37 weeks that X-ray diagnosis may be of assistance". Why then is he personally "relieved to find that even some of its earlier advocates have now discarded this type of examination?"

Again, immediately after this admission he states that "at this stage accurate clinical diagnosis can be difficult . . ." Yet he does not suggest that, because clinical diagnosis can be difficult, clinical examination should be given up. Quoting me, he says that because I deny that a single lateral view is adequate for the radiological diagnosis of the placental site (and emphasise the point by stating that, "even with four films, carefully planned, really adequate opinion is, not infrequently, very difficult to offer, even in expert hands") and because I lay stress on the *difficulty* of precise diagnosis, I have completely condemned this method of examination. If this use of a quotation out of context can be termed "argument", I still do not accept it.

Professor Macafee says that placentography has not been done for some years in his hospital. Such a statement hardly qualifies him to argue with those who still use the method daily. May I remind him that no radiologist sends himself cases: it is his colleagues who continue to refer cases to him because they believe that he can show the placental site accurately. Professor Macafee may be interested to know that since 1954 a single obstetrical unit, situated some 4 miles from Saint Mary's Hospitals, has referred an average of 56 cases per annum (in-patients as well as outpatients) for demonstration of the placental site. Already the indications are that this average will be exceeded in 1960. Apart from this, placental-site requests at Saint Mary's Hospitals amounted to 265 in 1959. These figures do not suggest that the method has fallen, or is falling, into disrepute.

Professor Macafee is very far from the truth if he thinks that those obstetricians who have an intimate up-to-date knowledge of expert radiological diagnosis "completely condemn" the method. He should come and see for himself exactly how the method can be used to his advantage, and thereafter attempt to convince my obstetrical colleagues of the error of their ways in referring cases for radiological demonstration of the placental site.

Department of Radiology,
Saint Mary's Hospital,
Manchester, 13. J. BLAIR HARTLEY.

ORAL CONTRACEPTIVES

SIR,—It should be clearly stated that the orally active progestational steroids have been in continuous use as a contraceptive in Puerto Rico for only four years. Whilst Dr. Mears (Feb. 27) is correct in stating that so far no harmful effects have been reported, it should be remembered that their use as an oral contraceptive will involve interrupted administration over a woman's entire reproductive life. Many more years of experience will have to be acquired before it can be safely stated that they are free from serious harmful effects, such as carcinogenic changes. Even after many years of experience with œstrogenic steroids, there is doubt about this point in the minds of several authorities.

It should also be pointed out that these substances can at present be obtained free of prescription (though a recent recommendation of the Poisons Board [1] seeks to limit them to issue on medical prescription). Whilst the limited clinical trials in their use as an oral contraceptive planned in this country will no doubt be conducted under the strictest medical supervision, the dosage and method of administration are being freely discussed in the Press, and there is nothing to stop a woman from trying out their use for herself, without medical supervision.

This group of compounds is certainly not free from side-effects which can include breakthrough bleeding, nausea, headache and dizziness, breast soreness and skin rash, and masculinising effects with some of the compounds available. Marked change of libido is common and I have found them of considerable value in this respect for the treatment of nymphomania.

It is clear that the experimental use of these compounds as an oral contraceptive is only justifiable under strictest medical supervision, and action should be taken to have these compounds included under category III of the Poison Schedule along with œstrogenic steroids, to insure that these cannot be used indiscriminately.

London, W.1. G. BARRY CARRUTHERS.

SIR,—Although long threatened I hope some others groaned to learn from the daily Press that an oral contraceptive had reached clinical trial in Birmingham. Dr. Mears added to the gloom until she hopefully said that these drugs are not really suitable for prescribing at present, only to relapse in her last paragraph by admitting "we" are looking for something simpler and less expensive, for use in large-scale population control in undeveloped countries. It is ironic that we in the West are only contemplating this measure at all because we are ourselves a sprawling population and, I suppose, undeveloped as well, but that is not my real point.

This method of birth control contains two offences against humanity which other methods do not have. The first offence is suppression of normal physiological function. I see no difference in this approach from the requests of those earnest young men who occasionally arrive in the consulting-room and ask if their vasa can be tied. We are surely agreed what we do with them: say no, politely, and if that fails to sink, ask them what kind of animals they think we operate on.

1. See *Lancet*, Feb. 20, 1960, p. 446.

The method secondly offends by not being an open and unconcealed contract between the parties. It is possible that either the man or woman could see that the pill is taken or given surreptitiously without consent or knowledge of the other, or worse, it could be given by an outside agent either for public or private purposes.

These are basal offences which it is difficult to reconcile with any code of morals hitherto held in this end of Europe. The other complications, such as genital or mammary cancer, risk of mutation, &c., would presumably be found out later; but it seems to me that a profession which is prepared to handle this drug in this country is betraying a sacred heritage. The opportunity is still open—refuse now to handle it, before it is too late.

Manchester. OLIVER JELLY.

HYDROCHLOROTHIAZIDE AND DIABETES INSIPIDUS

SIR,—Kennedy and Crawford [1 2] reported that in two cases of diabetes insipidus treatment with chlorothiazide or hydrochlorothiazide resulted in 50% reduction in urinary volume. They observed that a similar effect in hypophysectomised rats did not depend on adrenal cortical function. We have treated an 18-year-old male patient with a true diabetes insipidus with chlorothiazide (2 g. daily) and hydrochlorothiazide (75 mg. daily) observing the same effect reported by Kennedy and Crawford. The effects during the period of treatment are summarised below and in the accompanying figure:

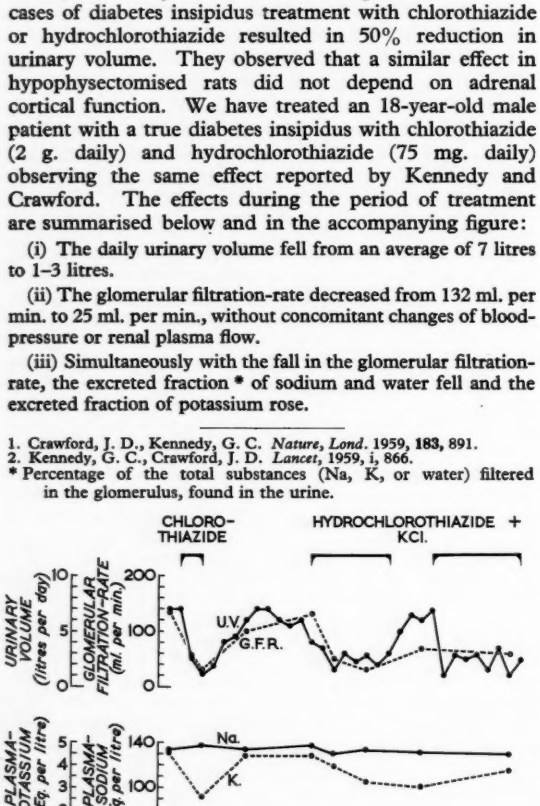
(i) The daily urinary volume fell from an average of 7 litres to 1–3 litres.

(ii) The glomerular filtration-rate decreased from 132 ml. per min. to 25 ml. per min., without concomitant changes of blood-pressure or renal plasma flow.

(iii) Simultaneously with the fall in the glomerular filtration-rate, the excreted fraction * of sodium and water fell and the excreted fraction of potassium rose.

1. Crawford, J. D., Kennedy, G. C. *Nature, Lond.* 1959, **183**, 891.
2. Kennedy, G. C., Crawford, J. D. *Lancet*, 1959, i, 866.

* Percentage of the total substances (Na, K, or water) filtered in the glomerulus, found in the urine.



Changes in urinary volume, glomerular filtration-rate, plasma-sodium and plasma-potassium, sodium, potassium, and water excreted fractions, and blood-pressure of a patient with true diabetes insipidus, treated with chlorothiazide (2 g. daily), hydrochlorothiazide (75 mg. daily), and potassium chloride (2 g. daily).

(iv) Plasma-sodium concentration remained unchanged, while plasma-potassium decreased sharply, inducing a secondary hypokalæmic alkalosis.

(v) The decrease in glomerular filtration-rate induced by hydrochlorothiazide was only partially restored after the subcutaneous administration of 30 units of aqueous pitressin which induced a large increase in the excreted fraction of sodium and did not change the excreted fractions of water and potassium.

These effects on renal function were maintained throughout the treatment period—i.e., no escape phenomena were observed. The total recovery of diuresis followed 2 days after the drug was stopped, and the effect on glomerular filtration-rate persisted for 4 to 6 days.

These results support the view that the paradoxical effect of this diuretic drug in diabetes insipidus is due to a decrease in glomerular filtration-rate to much below normal.

J. J. Aguirre Hospital, University of Chile, Santiago, Chile.

M. PLAZA DE LOS REYES
R. GÓMEZ
I. BRADFORD.

A PLEA FOR MORE NECROPSIES

SIR,—As an answer to the difficult problems of diagnosis is usually found in a postmortem examination, it may be of interest to record the results of 223 necropsies on patients from the geriatric wards of Tooting Bec Hospital. The diagnosis during life was corroborated after death in 212 cases, so that 11 remained in which either a wrong diagnosis had been made or important conditions were revealed that had escaped observation during the patient's life.

(1) Aged 74. Sudden death from coronary thrombosis verified at necropsy. A carcinoma of the sigmoid colon was unexpectedly found.

(2) Aged 55. Here again coronary thrombosis was given as cause of death. The patient had craniovascular syphilis with pareses and seizures. Necropsy revealed a gastric carcinoma.

(3) Aged 75. Ten days after admission with no history of pulmonary disease, the patient died, apparently of bronchopneumonia. At necropsy consolidated and caseating tuberculous lesions of the lungs came to light.

(4) Aged 62. Lobar pneumonia (cause of death) was combined with cirrhosis of the liver, which had not been detected during life.

(5) Aged 76. A diabetic had an apoplectic seizure six weeks before he died, death being attributed to cerebral thrombosis. Necropsy showed an undiagnosed primary carcinoma of the liver without secondary growths.

(6) Aged 70. Cerebral hæmorrhage was associated with a hæmangiomatous angioplastic meningioma occupying a third of the rostral part of the right temporal lobe.

(7) Aged 91. Senility was given as the sole cause of death. Necropsy disclosed carcinoma of the prostate with masses of metastases in the liver and one in the cortex of the left kidney. The right kidney showed hydronephosis.

(8) Aged 85. In this case of chronic lymphatic leukæmia a previously undiagnosed carcinoma of the stomach was found.

(9) Aged 93. This patieht in whom only chronic bronchitis had been diagnosed in life was found at necropsy to have an oat-cell bronchial carcinoma spreading through the lung tissue, and a metastasis in one adrenal gland.

(10) Aged 74. A senile dement was admitted with the diagnosis of carcinoma of the bladder with cerebral metastases. Postmortem examination revealed a benign papilloma of the bladder and a moderately enlarged non-malignant prostate with localised abscess formation. The brain presented no abnormality except senile vascular changes.

(11) Aged 75. In this patient, who died of bronchopneumonia and cardiovascular degeneration, a diaphragmatic gastric hernia was unexpectedly discovered at necropsy.

The number of diagnostic failures (roughly 5% out of 223) discovered post mortem is comparatively small, but these errors and omissions would undoubtedly be revealed in increasing numbers in the many cases where the cause of death has not been verified by necropsy.

In no less than 6 of these cases some unsuspected form of

cancer was discovered at necropsy. Otherwise, the cause of death would probably have been given as cardiovascular degeneration. Statistics for the causes of death in general and for malignant disease in particular thus cannot claim any degree of accuracy, and yet statistics are held to be an important basis for research and preventive medicine.

It seems that more use should be made of postmortem examinations. It may be necessary to overcome the traditional objection of the public to necropsy, but if the assurance is given that the human form is treated with respect and reverence, and if it is explained that there is great benefit for the living to be gained from examination of the dead, it should be possible to overcome prejudice.

Geriatric Department,
Tooting Bec Hospital,
London, S.W.17. NOEL ALDER.

TREATMENT OF ORGANOPHOSPHORUS POISONING

SIR,—Among the supportive measures mentioned by Edson [1] are postural drainage and oxygen for the relief of pulmonary œdema and respiratory distress. In the most severe and acute poisoning, with predominant asphyxia, only tracheal intubation, active ventilation, and bronchial aspiration can preserve life until atropine and other medical measures become effective.

We have treated in this way 5 persons poisoned by parathion.

They arrived at hospital on the point of death and 3 of them were saved. Muscular relaxation and a comatose state make it easy to intubate without curare, and the tube is well tolerated even when consciousness and spontaneous breathing return. In 1 case a tube was kept in successfully for twelve hours.

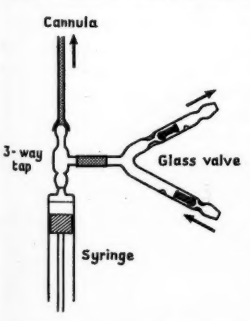
We believe that many deaths might be avoided by these simple measures, which gain in efficacy if applied immediately the patient enters hospital.

Ospedale Civile di Oristano,
Cagliari, Italy. GIULIANO TESTA.

A VALVE FOR EXCHANGE TRANSFUSIONS

SIR,—For the past 2½ years at this hospital we have been using a 2-way automatic glass valve in performing exchange transfusions on babies, together with one 3-way metal tap (see figure). We have found it extremely satisfactory.

Its only defect is a slight increase in the dead space, but this has no practical effect on the exchange. It is, of course, only a gadget, but it is labour-saving and allows the operator to have the tap less on his mind.



The valve was first designed by Dr. Henry W. Kaessler, of New York, and was made and distributed by the Ringler-Rados Surgical Corp., 3958, Broadway, New York, 32, who have kindly allowed this valve to be made and marketed in this country. The valve is now obtainable from the Laboratory Glassblowers Co., Valley Works, Lane End Road, Sands, High Wycombe, Bucks, at a cost of 21*s*. It is not identical with the American model, but it has proved satisfactory, and I think is well worth the attention of all those who have to do exchange transfusions.

When using the valve the bottle containing the blood must be at a lower level than the valve itself or siphoning back will occur.

It should be noted that syphoning from the catheter into the waste tube may occur if the syringe is removed from the tap. The waste tube must always be clamped before removing the syringe.

Queen Charlotte's
Maternity Hospital,
London, W.12. A. P. NORMAN.

ACUTE HÆMOLYTIC ANÆMIA AND PHENACETIN

SIR,—In connection with Dr. Houston and Dr. Barlow's report [1] I should like to record a similar experience.

The patient was a charwoman, aged 28, with no family history of nervous or mental diseases, whose childhood, home, and marriage had been unhappy. At the age of 17 she had shown X-ray evidence of peptic ulcer. After an acute psychic trauma concerned with a new love-affair, she consumed 60 'Diallyphen' tablets containing 30 g. phenacetin (plus 1·8 g. allobarbitone).

Admitted to hospital about 12 hours later, on Aug. 12, 1959, she was deeply unconscious and cyanosed, with deep frequent respiration. Her pupils were medium-sized, reacting to light. Reflexes normal. Blood-pressure 100/80 mm. Hg, pulse-rate 108. Shortly after admission, she was given methylene-blue, after the blood had been found to contain 51% methæmoglobin. She gradually rallied, and on the 5th day she was completely orientated. Since, however, the hæmoglobin level was rapidly decreasing, the erthyrocyte sedimentation-rate rising, and jaundice increasing, with dark urine and normally coloured stools, the hæmolytic anæmia was treated with prednisone and she made a rapid recovery. Steroid therapy was withdrawn after 17 days, and she was discharged in good health. Hæmoglobin level and reticulocyte count two weeks after discharge were normal.

Hillerød, Denmark. KLAUS VOLLMOND.

"LIES, DAMNED LIES, AND STATISTICS"

SIR,—Disraeli's triad is a witty expression of the commonly held opinion that "you can prove anything by statistics". Be that as it may, statistics very largely govern medical and other forms of scientific research, in spite of doubts which may arise in the minds of the "good doctor" and the experienced clinician, who sometimes have the intuition that many factors of importance transcend the realm of ponderables.

Many doctors have expressed doubts about the general applicability of statistical conclusions, and, still speaking from a medical rather than a lay point of view, I should like to contribute to the case that "you can prove anything by statistics". The reasons for holding such a view are broadly as follows:

The validity of statistics never transcends the limits set by the criteria initially chosen to define a given study. These criteria naturally determine the data obtained, and these data alone constitute the raw material from which the statistical generalisations (or "probabilities") finally emerge. The most important point here, albeit a simple one, is that the criteria chosen directly govern the end-results, which, so to speak, are a "function" of the former. (That is to say, the results can never be "greater" than the original criteria from which they derive.) A modification of the criteria clearly means an alteration in the results.

The main danger here is not simply that a deliberately weighted choice of criteria (calculated to satisfy some interest) is sufficient to secure results agreeable to that interest. (This is possible, and it can be difficult to detect.) Much more alarming, and more common, is what can occur even when the choice of criteria (in, for example, a clinical trial) springs from a would-be "objective" intention. (Nearly always such an intention is painfully naïve in operation.) In spite of would-be objectivity, the way here is inevitably wide open for major self-deception. The reason for this is as follows. The bio-

1. *Lancet*, 1959, i, 1204.

1. *Lancet*, 1959, ii, 1062.

logical situation, by its very nature, is always indefinitely complex. For this reason it is necessary to select a set of ponderables which is restricted to manageable proportions, and it is in the nature of things that this selection, however just the intention, cannot fail to be arbitrary. Explicit definition of the set of criteria selected for study is usually held to be a sufficient safeguard against subsequent misinterpretation. In many minds, however, statistical conclusions deriving from a limited set of "arbitrarily" defined criteria are allowed to spill over on to a much wider field of reference. Experience shows that it is all too easy to forget the limitations inherent in statistics by definition.

A point of more fundamental importance is that data collected for statistical analysis are as "quantitative" as can be, for the reason that "qualitative" overtones are not susceptible of measurement, and, as every quality is unique in itself, cannot be added to one another to form a series of "similars" (like numerical units), about which alone "mathematical" statements can validly be made. This exclusion of real, albeit immeasurable, factors is the reason why statistical results always exhibit a marked artificial character, which, if underestimated or unsuspected, can lead to conclusions which are both misleading and unrealistic.

I submit that woolly thinking on the question of statistics has become widespread and habitual, and that this state of affairs has had enormous repercussions on our life and knowledge in general. Scrupulously realistic scrutiny of statistical results and implacably clear thinking about the nature of statistics itself are urgent intellectual necessities.*

Manchester. W. S. STODDART.

PERTHES' DISEASE

SIR,—Our experience is quite contrary to Professor Trueta's statement (Feb. 13) that true Perthes' disease is exceptional in the Negro race. We say "true" Perthes' disease to draw a clear distinction between classical juvenile osteochondritis and the faintly similar changes found in the femoral heads of patients who have sickling disease; they are separate entities, and both certainly occur in the African.

University College Hospital, Ibadan. W. P. COCKSHOTT.
Mpilo Hospital, Bulawayo. P. E. S. PALMER.

LIPÆMIA AND FIBRINOLYTIC POTENTIALITY

SIR,—Dr. Hougie and Dr. Ayers (Jan. 23) state that we found that "the fibrinolytic activity of blood tends to be lower in people with a high serum cholesterol than in those with a lower level". Now, at the time we wrote the article [1] we had not done that experiment, but we have since, and are interested to note that Hougie and Ayers find as we have done that the cholesterol level has no effect on the level of fasting fibrinolytic activity.

In the work referred to by Hougie and Ayers, we artificially altered the cholesterol content of normal plasma with various solvents and found a relationship between the residual cholesterol and the fibrinolytic activity of the treated plasma.

It is of great interest and importance to note how small changes in technique alter the results of most of the current methods for estimating fibrinolytic activity. We left our clots in their own serum, and in the majority of cases there was still clot present after 24 hours' incubation at 37°C. Hougie and Ayers remove their clots from the serum, wash them in buffer, and leave them in buffer, and find considerable degrees of lysis, even up to 100%, in as short a time as 1 hour. This suggests that the serum and what it contains may be rather important when one wishes to study factors inhibitory to fibrinolysis when measured by a plasma-dilution technique.

Our most recent work (to be published) suggests that proactivator is activator bound by an inhibitor, a cholesterol- and triglyceride-containing protein. Proactivator, we find, has slight affinity for fibrin, but activator has marked affinity. On the lysis of the clot, activator is released again. Thus, I envisage that in Hougie and Ayers' method the activator is available over and over again for activation of plasminogen, also adsorbed on the fibrin, resulting in rapid lysis. The activator inhibitor is present in the serum and has been removed in their method, but not in ours, and this may account for the differing results.

Department of Hæmatology,
South African Institute for Medical Research,
Johannesburg. H. B. W. GREIG.

AUTOGENOUS VACCINES AND THE COMMON COLD

SIR,—May we refer briefly to the comments of Dr. Ritchie (Feb. 27) and Dr. Heald (March 5)?

A feature of Dr. Ritchie's trials was that the vaccines were prepared from unselected bacteria isolated from patients' own saliva. It seemed possible that his successful results were due to this rather than to his dosage schedule. The work which was undertaken on R.A.F. flying pupils was not intended to repeat the work of Dr. Ritchie. In our trial his method of vaccine production was copied but we realised that we could not expect healthy young men, who were in no way worried about colds, to volunteer for a long series of injections. Nevertheless, as the catarrhal complications of the common cold seriously interfere with flying, it seemed worth investigating a modification of Dr. Ritchie's scheme since his own results had suggested that the catarrhal stage could be reduced, even although the incidence of the primary infections were not. This was the advantage we sought, provided it could be achieved with a reasonably small number of injections. Although for practical purposes we were unsuccessful, we cannot agree with Dr. Ritchie that, because we found his method impracticable, we should not have investigated an alternative procedure.

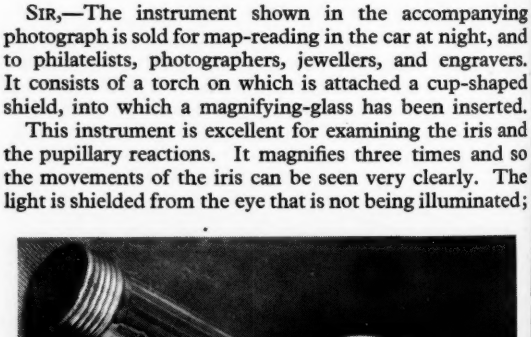
D. L. MILLER
J. S. WILSON
R. E. O. WILLIAMS
J. C. MCDONALD.

Central Public Health Laboratory,
London, N.W.9.

AN INSTRUMENT FOR EXAMINING THE PUPIL AND IRIS

SIR,—The instrument shown in the accompanying photograph is sold for map-reading in the car at night, and to philatelists, photographers, jewellers, and engravers. It consists of a torch on which is attached a cup-shaped shield, into which a magnifying-glass has been inserted.

This instrument is excellent for examining the iris and the pupillary reactions. It magnifies three times and so the movements of the iris can be seen very clearly. The light is shielded from the eye that is not being illuminated;



* For a full treatment of statistics from this point of view, see René Guénon's *The Reign of Quantity*, London, 1953.

1. *Lancet*, 1957, ii, 461.

and so the reflex movement from stimulating the contralateral eye can easily be elicited.

This instrument might be equally useful to dermatologists.

It is called Magniray Illuminated Magnifying Glass, it costs 26s. 6d., and it can be obtained from John Bell & Croyden, Boots, or from the importers, E. Herst, 14, Clifford Street, Bond Street, London, W.1.

National Hospital for Nervous Diseases,
Queen Square, London, W.C.1. P. W. NATHAN.

ACROPARÆSTHESIÆ AND THE CARPAL-TUNNEL SYNDROME

SIR,—Your annotation of Feb. 27 and the article by Dr. Wilkinson on the carpal-tunnel syndrome in pregnancy call for some comment.

The syndrome of acroparæsthesia, as defined by Kremer,[1] is a well-defined symptom-complex that has only one cause—namely, median-nerve compression in the carpal tunnel. Lesions in the vicinity of the thoracic outlet or axillary inlet do not cause anything like this group of symptoms, and I think it is a pity that this mythical entity has been disinterred so soon after it has been buried. Symptoms of cervical-root compression in cervical spondylosis are usually easily distinguished from acroparæsthesia, but the two conditions are very common and it is not strange that they occasionally coexist. However, Dr. Wilkinson's finding of root signs in 7 out of 14 cases of acroparæsthesia in pregnancy is surely very unusual and is a much greater incidence than I personally have found.

Dr. Wilkinson treated 3 cases with splinting of the wrist and in only 1 was there a good result, but I have treated many such cases with splinting, and in my view it is the treatment of choice for acroparæsthesia in pregnancy.

London, W.1. K. W. G. HEATHFIELD.

SCREENING TEST FOR TYPHOID CARRIERS

SIR,—In a recent paper,[2] Schubert, Edwards, and Ramsey described the extraction of Vi antigen from *Citrobacter ballerupensis* (*Salmonella ballerup*) by hot saline. According to these authors, sheep erythrocytes exposed to such an extract absorbed the Vi antigen and thus provided a reagent that was sufficiently sensitive and specific to be useful for a Vi hæmagglutination screening test for the detection of typhoid carriers. In view of the apparent attractions offered by the procedure described—ease of preparation of the antigen and specificity of the test as reported in the paper—I think that it is worth while to give a résumé of my findings during a trial of this method.

It was found at an early stage that a high proportion of the human sera tested contained agglutinins for sheep erythrocytes. As it was impracticable to carry out a preliminary absorption of these agglutinins, human group-O Rh-negative erythrocytes were substituted for sheep cells. In all other respects the hæmagglutination tests were carried out as described by Schubert et al. It was confirmed that sera known to contain Vi antibody agglutinated the sensitised erythrocytes. However, while Schubert et al. did not report any false-positive hæmagglutination reactions in their control series, I found, with more than 300 sera from randomly selected "normal" persons, that 20% gave positive reactions with the sensitised red cells. In contrast, only about 1% of these sera were regarded as positive in the routine agglutination test with a suspension of *Salmonella typhi* ViI. Human erythrocytes sensitised with purified Vi antigen yielded results similar to those of the ViI suspension. In the majority of instances, the antibody causing agglutination of Ballerup-sensitised erythrocytes in normal sera was not absorbed by ViI suspension or neutralised by pure Vi antigen. Controls of the human erythrocytes which had not been exposed to Ballerup extracts were invariably negative.

1. Kremer, M. *Lancet*, 1953, i, 590.
2. *J. Bact.* 1959, 79, 648.

The conclusions may therefore be drawn that the antibody that agglutinated the Ballerup-sensitised red cells in the normal controls was not a Vi antibody; that the saline extract of *Citrobacter ballerupensis* contains antigens (perhaps O antigens) in addition to the Vi antigen; and that these additional antigens are adsorbed to erythrocytes, thus introducing a sensitivity which is not connected with the Vi antigen and its corresponding antibody.

As about 20% of the sera of normal persons in this country appear to contain antibodies to these non-Vi antigens, the test is clearly unsatisfactory for use here.

These findings will be reported in detail at a later date.

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London, N.W.9. E. S. ANDERSON.

METHYLTHIOURACIL IN THYROTOXICOSIS

SIR,—Professor Wayne's references (Feb. 20) to methylthiouracil prompt me to record the long-term follow-up of 100 consecutive cases of thyrotoxicosis personally treated with this drug when it was in vogue between the years 1947 and 1954.

Treatment was maintained for a year with regular outpatient observation for a further year and intermittently thereafter. Thyroidectomy was suggested if signs of relapse occurred, and also to any patient who had a large goitre as soon as he or she became euthyroid. There were 90 women and 10 men, the average age being 55. The results, surveyed this year, are as follows:

Well after discontinuing treatment	43
Thyroidectomy for relapse or goitre	37
Continuing treatment, refusing operation	13
Lost from follow-up	4
Dead, while on treatment (carcinoma of breast, cerebral embolus, degenerative cardiac failure)	3

No case of agranulocytosis occurred. Treatment only had to be stopped once, for drug rash and fever, but it was possible to resume again after an interval. The fatal case of cerebral embolus arose during the change from fibrillation to sinus rhythm; quinidine had not been given. Auricular flutter, which has been erroneously described as a toxic effect of antithyroid drugs, was noted twice in the transition from fibrillation to sinus rhythm. It is, of course, not a toxic effect, but a consequence of the mechanism by which this change is achieved.

The chance of relapse increases with the period of observation, but it is clear that an appreciable number of patients get a worthwhile remission on this drug. Even if it is necessary to give a second course at some later crisis in their lives, they may prefer it to thyroidectomy.

St. Helier Hospital,
Carshalton. C. P. PETCH.

POTASSIUM PERCHLORATE IN THYROTOXICOSIS

SIR,—In their article of Feb. 20 on the relative merits of various anti-thyroid drugs, Dr. Crooks and Professor Wayne describe a case where agranulocytosis developed during the third week of treatment with potassium perchlorate in a dose of 1500 mg. a day. Later they say: "If the use of potassium perchlorate increases we should not be surprised to learn that this serious condition may be associated with lower doses or that the bone-marrow may be affected in other ways."

In the following case both agranulocytosis and thrombocytopenia occurred after twelve days' treatment with 1000 mg. a day in divided doses.

The patient was a married woman, aged 56, suffering from classical Graves' disease. The basal metabolic rate (sedated) was +56% before treatment. On Feb. 7 treatment began with potassium perchlorate 1000 mg. daily. At this time her white-cell count was 5000 per c.mm. She remained well until Feb. 19, when she developed a high temperature, fol-

lowed by a punctate erythema on the extensor surfaces of her limbs two days later. The white-cell count on Feb. 21 was 2000 per c.mm. (polymorphonuclears 1200). Treatment with potassium perchlorate was stopped on Feb. 22 when the total polymorphonuclear-count was 980 per c.mm. and platelets 60,000 per c.mm. A marrow puncture on the same date showed some toxic changes in the granulocyte precursors, no evidence of any maturation arrest, but a prominent number of eosinophils. The rash subsided on Feb. 24. By Feb. 29 the total polymorphonuclear-count had risen to 3250 per c.mm and the platelets to 100,000 per c.mm. The platelet-count was 220,000 on March 4 and the polymorphonuclear-count was 4850. The temperature returned to normal on March 3.

She was receiving no other drugs that might have caused these hæmatological abnormalities.

NEVILLE SOUTHWELL
KEITH RANDALL.

London, W.1.

EARLY DIAGNOSIS OF PREGNANCY

SIR,—A few months ago, I read with great interest your correspondents' letters on tests for the early diagnosis of pregnancy. Dr. Forster [1] and Dr. Kenton [2] described the use of oral or parenteral hormones, whereas Dr. Hobson [3] summarised 12 years' experience with Hogben tests, and Dr. MacDonald and Dr. Sharman [4] described a diagnostic method based on the examination of cervical mucus.

At the time these letters appeared, I was investigating still another technique for early pregnancy diagnosis and, as I have now completed a series of 100 tests, I should like to present a summary of my results.

As Dr. Forster stated, the urinary gonadotrophic tests have certain disadvantages; and, for this reason, I have been trying to find a simple, safe, and inexpensive method for diagnosing early pregnancy in general practice. In other countries the use of cholinergic drugs such as neostigmine (' Prostigmin ') and pyridostigmine (' Mestinon ') has had considerable vogue. The original method consisted in giving an intramuscular injection of one of these drugs on three consecutive days; and, if the patient was not pregnant, menstruation was said to take place within 72 hours of the last injection. For a general practitioner, the need to use the drug by injection was a disadvantage of this method. In 1956, however, Bartolomei and Mincato [5] reported a series of 47 patients with amenorrhœa in whom pyridostigmine (180 mg. daily by mouth) was used as a pregnancy test, with accurate results in all except 2 patients.

I have now carried out a trial with oral pyridostigmine in 100 consecutive cases of amenorrhœa seen in my practice. The age-distribution of the patients and the duration of amenorrhœa were as follows :

Age (years)	*No. of cases*	*Amenorrhœa (weeks)*	*No. of cases*
16–23	38	0–2	16
24–31	33	3–5	63
32–39	21	6–8	21
40–48	8	—	—
Total	100	Total	100

The dose of pyridostigmine was one tablet (60 mg.) three times daily for three consecutive days. The test was considered " negative " if the patient menstruated within one week of the last dose. The results were:

Days after test	1–2	3–4	5–7	*Total*
Menstruated				
' Negative ' results	47	31	5	83
Failed to menstruate				
' Positive ' result	—	—	—	17

Of the patients in whom the test was " negative ", menstruation appeared normal; in no case was there evidence that a pregnancy had been interrupted, though admittedly this cannot be proved. The same is true of pregnancy tests based on the use of hormones.

Of the 17 patients who failed to menstruate, 14 were later shown by follow-up clinical examinations to be pregnant. There were 3 " false positives "; 2 were in menopausal patients (aged 45 and 47 respectively) and 1 was in a girl aged 21 with an infantile uterus. The test was thus 100% accurate when negative, and 82% accurate when positive, giving an overall accuracy in 100 cases of 97%. The only side-effects were complaints of nausea by 1 non-pregnant and 2 pregnant women.

The test was thus shown to be simple, accurate, and inexpensive, the basic N.H.S. cost for a course of pyridostigmine tablets for one woman being about 3*s*.

Bournemouth. GABRIEL V. JAFFÉ.

1. Forster, D. H., *Lancet*, 1959, ii, 242.
2. Kenton, R. J. *ibid.* p. 409.
3. Hobson, B. M. *ibid.*
4. MacDonald, R. R., Sharman, A. *ibid.* p. 566.
5. Bartolomei, G., Mincato, C. *Attual. ostet. ginec.* 1956, **2**, 1354.

CHOLESTERYL ESTER FATTY ACIDS IN ATHEROMA AND PLASMA

SIR,—Reading again Dr. Sinclair's explanation [1] of the controversy concerning the relative deficiency of essential fatty acids (E.F.A.) and the data of the analyses of atheromatous plaques, I should like to suggest a second possibility.

The E.F.A. after having passed the intestinal wall will readily esterify " available " cholesterol, which is known to have a great affinity for unsaturated fatty acids. Cholesterol synthesis occurs in many organs. If the organ E.F.A. content is too low, the possibility exists that less cholesterol than " normal " is esterified, or that esterification occurs with unusual fatty acids. As soon as contact takes place with the newly absorbed E.F.A. in the blood or chyle (whether free or not), the energetically more stable esters can be formed.

The physiological " normal " esters must be assumed to be the more stable, though there may be others, such as those mentioned by Dr. Sinclair, with an equal stability. The resulting esterification of free cholesterol and/or exchange of fatty acids are extracellular processes, the latter could concern phospholipids as well. The excess of blood-lipids deposited in the vessel walls will then have an appreciable E.F.A. content, which will decrease significantly only when E.F.A. deficiency is considerable.

As a consequence of the extracellular " abuse " of E.F.A. only little—and apparently often too little—is left for intracellular use, which means that cholesterol turnover, and breakdown especially, are inhibited (among other intracellular activities). Perhaps it is better to say are inhibited further, since there was already an intracellular shortage of E.F.A. Only by supplying large amounts of E.F.A. can this vicious circle be broken and intracellular activity speeded up to normal, thus removing cholesterol, lowering serum-cholesterol, &c.

That increase of cholesterol turnover and removal follows E.F.A. administration has lately been demonstrated.[2–4] Tissue E.F.A. analysis, especially of liver, may help in solving the problem.

A further complicating factor could be found in the observations that fat-free and E.F.A.-deficient diets cause an increase in trienoic content of storage fat,[5] egg-yolk fats and phospholipids,[6] rat mitochondria and microsomes,[7] rat heart and testis fatty acids,[8] together with a decrease in dienoic acids. This trienoic was suggested to be partially hydrogenated arachidonate.[9] On supplying the polyunsaturated fatty acids (corn oil), trienoic contents decreased and dienoic increased again.[5 6] (It is but a step to speculate on a connection with the observation of Keys et al.,[10] who found an increase in serum-cholesterol in man after oral ingestion of arachidonic acid.)

Netherlands Institute of Nutrition, Amsterdam. L. M. DALDERUP.

1. Sinclair, H. M. *Lancet*, 1959, ii, 789.
2. Gordon, H., Lewis, B., Eales, L., Brock, J. F. *ibid.* 1957, ii, 1299.
3. Lewis, B. *ibid.* 1958, i, 1090.
4. Hellman, L., Rosenfield, R. S., Insull, W., Ahrens, E. H., Jr. *J. clin. Invest.* 1957, **36**, 898.
5. Reiser, R., Gibson, B., Carr, M. J., Lamp, B. G. *J. Nutr.* 1951, **44**, 159
6. Rieckehoff, I. G., Holman, R. T., Burr, G. O. *Arch. Biochem.* 1949, **20**, 331.
7. Klein, P. D., Johnson, R. M. *Fed. Proc.* 1953, **12**, 231.
8. Aaes-Jørgensen, E., Holman, R. T. *J. Nutr.* 1958, **65**, 633.
9. Maclean, I. S. The Metabolism of Fat. London 1943. (Refs. 5, 6, 7, 9 cited by Deuel, Jr., H. J. The Lipids; vol. III, p. 371.)
10. Keys, A., Anderson, J. T., Grande, F. *Amer. J. clin. Nutr.* 1959, **7**, 444.

B.M.A. OR A.M.B.?

SIR,—We wholeheartedly support the opinion in your leading article of March 5 that the profession needs an "association of medical bodies", both to give the various branches of medicine balanced representation and to develop a collective responsibility above that of sectional interests.

You rightly point out that the British Medical Association is widely regarded as primarily representing general practitioners, even though they are a minority of its total membership (20,000 out of 74,000). We do feel, however, that the policy of the B.M.A. does not always truly represent even the conflicting interests within general practice, and in particular those between large-list and small-list practitioners and between principals and assistants. It is the lack of overall satisfactory representation for many in the profession that has led to the appearance of special groups within the B.M.A., and, as in our case, of independent bodies, to represent minority sections.

Machinery to facilitate an exchange of views by representatives from the various sections of the profession might help towards a solution of some existing problems (e.g., improving the prospects for registrars and senior registrars). It might also lead ultimately to a confederation of the different medical bodies, to the advantage of the profession as a whole and the future of the Health Service. The first step, however, presents a major difficulty.

A. C. MCLEISH
H. P. HILDITCH
J. J. SEGALL.

General Practice Reform Association,
London, N.W.6.

BRETYLIUM TOSYLATE IN THE TREATMENT OF HYPERTENSION

SIR,—Dr. Evanson and Dr. Sears (March 5) referred to "unexplained exertional dyspnœa" in patients on bretylium tosylate; and Turner and Lowther (Feb. 13) noted "dizziness not due to postural hypotension". We feel that both these may be due to exertional hypotension which we have noted in a number of patients on the drug.

A fall in blood-pressure on exertion has been previously observed with hexamethonium,[1] and with guanethidine.[2] Our experience in the use of bretylium has shown that this phenomenon is of considerable clinical importance and may be a bar to satisfactory control of blood-pressure in some patients.

Of 112 patients receiving bretylium, 19 have had symptoms on exertion sufficient to cause some disability. The symptoms complained of were: faintness, giddiness, or dizziness (11 cases), muscular weakness (4), and breathlessness (4). 4 of these patients have been so disabled that they were unable to carry on their work or normal household duties or climb up one flight of stairs without resting. 1 patient was even unable to dress himself.

We have measured the blood-pressure before and immediately after exertion in 13 of these patients. 11 of them showed falls of pressure ranging from 15/25 to 160/80 (mean fall 59/47 mm. Hg). The exertion consisted of walking slowly upstairs until the symptoms occurred; usually only one flight was necessary. Of 6 control patients who were taking bretylium without exertional symptoms, only 1 showed a fall in pressure after four flights of stairs.

In 4 of these patients a considerable exertional fall of blood-pressure occurred in the absence of any postural fall. Blood-pressure readings from the two most striking cases were: (*a*) lying B.P. 225/165, standing 210/170, after one flight of stairs 120/90; (*b*) lying 240/140, standing 250/150, after one flight of stairs 90/70.

The mechanism of this effect is as yet obscure. 2 patients who had exertional hypotension on bretylium showed the same effect on guanethidine. We suggest that it may be due to a failure to increase the cardiac output with exercise.

University College Hospital Medical School, London, W.C.1.

R. D. LOWE
M. L. ROSENHEIM.

1. Ronnov-Jessen, V. *Lancet*, 1953, ii, 706.
2. Leishman, A. W. D., Matthews, H. L., Smith, A. J. *ibid.* 1959, ii, 1044.

PULMONARY DIFFUSING CAPACITY

SIR,—The letters (Feb. 6) from Dr. McNeill and Dr. Ogilvie raise two points in the technique of the single-breath method of measuring the pulmonary diffusing capacity (D_L)—first, the size of sample collected, and second, the time of collection.

Dr. McNeill says that in modifying the single-breath test for measuring the D_L we have made an erroneous assumption about the way in which the expired air is usually collected. In fact, no such assumption was made, for it is clear from the literature [1–6] that there is considerable uncertainty as to which portion and how much of the expired gas is collected.

We started by accepting the fact observed and discussed by Ogilvie, Forster, and others [1 4 7] that the diffusing capacity varies with the length of breath-holding. We offered theoretical and experimental evidence that such variations in normal subjects are due to experimental technique and not to regional inequality of lung function.

Dr. McNeill's statement that only 300 ml. is required suggests that he is confusing the volume needed for analysis of the gas with that actually collected; for it is clear from their section on "method", that Ogilvie et al.[4] collected a much bigger sample. They state that "all of this expiration except the first litre is collected in a bag", and Forster et al.[1] that the subject "rapidly expired to residual volume turning (the) tap to collect the sample after a litre or more of gas had been expired". Dr. Ogilvie in his letter says that, "providing that the subject is told to expire with all his might, he will add little to the sample after 2 or 3 seconds". We conclude that, with the exception of the first rejected litre, the greater part of the expirate, almost to residual volume, is sampled. A simple calculation shows that in order to sample only 300 ml. in the early part of a maximum expiration of a normal subject would require an ability to manipulate the tap twice within approximately $^1/_6$ second.

That samples of more than 300 ml. were actually used by Forster et al. is confirmed by our finding that when a large sample (2·6 litres) is collected, our results for the effect of changing the breath-holding time were superimposable (after allowing for an 8% difference in diffusing capacity) on those published by Forster. However, when we used a sample of 85 ml. virtually no variation with breath-holding time was observed. Thus we conclude that large samples must have been used in Forster's original experiments.

Dr. Ogilvie also states that our correction to his data would result in a change of only about 5%. If the sampling-times are 1–2 seconds, such alterations would approximately be 5–10% at a 10-second breath-holding time, but 10–20% for a 5-second breath-holding time, which is often as much as disabled subjects can do. In addition, if there is a considerable change in alveolar volume, attendant upon either a large or a late sample, there is an error due to this which is not corrected by the simple allowance for sampling-time, so that the total error may be much larger than the 5% suggested.

In patients with obstructive disease the effect of alveolar volume change may be small, but as the sampling-time in these cases may be as long as 4 seconds, the correction for this time becomes even more important, especially as such subjects are also those who are often unable to hold their breath for more than a few seconds. Such short breath-holding times may also apply when the test is used on normal subjects when exercising.

1. Forster, R. E., Fowler, W. S., Bates, D. V., Van Lingen, B. *J. clin. Invest.* 1954, **33**, 1135.
2. Forster, R. E., Cohn, J. E., Briscoe, W. A. S., Blakemore, W. S., Riley, R. L. *ibid.* 1955, **34**, 1417.
3. Bates, D. V., Pearce, J. F. *J. Physiol.* 1956, **132**, 232.
4. Ogilvie, C. M., Forster, R. E., Blakemore, W. S., Morton, J. W. *J. clin. Invest.* 1957, **36**, 1.
5. McNeill, R. S., Rankin, J., Forster, R. E. *Clin. Sci.* 1958, **17**, 465.
6. McGrath, M. W., Thomson, M. L. *J. Physiol.* 1959, **146**, 572.
7. Forster, R. E. *Physiol. Rev.* 1957, **37**, 391.

We are, therefore, convinced that it is necessary to use small early samples (< 1 litre) when allowance for the time of sampling can be made. In this way a considerable improvement in both repeatability and validity is achieved. The summation of such errors may be sufficient to explain a situation which has recently come to our notice, in which a normal man was tested in one laboratory and found to have well over 100% predicted value. Tested in another laboratory a few days later, he was told that his value, alas, was only 60% of expected.

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(Medical Research Council),
Llandough Hospital,
Penarth, Glamorgan.

R. S. JONES
F. MEADE.

PRIVATE PATIENTS IN THE NATIONAL SCHEME

SIR,—I have followed with great interest the lengthy correspondence on this subject. There are several points which require answering.

Why do patients who are entitled to treatment under the terms of the National Health Service seek private treatment at all? In my view it is neither the social aspect nor the so-called snob value but the time factor which counts.

My own practice has been entirely amongst the elderly who come to me because I am prepared to spend the necessary time on them, and listen patiently to what they have to say. When these same people go to their N.H.S. doctor's surgery he is probably busy and they have to wait their turn. When it does come they have to collect themselves and walk into the doctor's presence—a slow business. Then they have to explain what they have come about and receive attention: all this takes time in a busy surgery. This type of patient, I believe, forms the majority of private patients these days.

It will be a bad day for British medicine when private practice ceases to exist; everything should be done to encourage it. Please do not let us hear any more of its social or snob value.

Worthing. HAROLD LEESON.

OVERDOSAGE OF PHENELZINE SULPHATE

SIR,—Dr. Sclare and Dr. Atkinson (Jan. 30) raise the question of overdosage of thymoleptic drugs and outpatient regulation of their administration.

An admittedly limited experience of these drugs gives the impression that whether they should be started on in outpatients depends on the presence of a premorbid stable personality structure and the absence of an underlying delusional system. It seems that where the depressive affect or anergy is primary then outpatient treatment is desirable, depending of course on the severity of symptoms. Secondary mild delusional ideas or hypochondriasis would obviously not contraindicate this; if treatment is successful they will disappear with the primary symptoms. If these two conditions are not fulfilled, however, it seems prudent to admit the patient to hospital to determine the maintenance dose and feasibility of continued treatment, since these drugs, contrary to a recent statement [1] that they appeared to have "little significant action beyond placebo effect", are indeed powerful in action in many patients and can produce startling not to say alarming results.

The following case illustrates this point.

A man of 24 was admitted to this hospital some two and a half years ago in acute mania after taking iproniazid ('Marsilid') five tablets a day (admittedly beyond the manufacturers' recommended dose). He was diagnosed as "chronic undifferentiated schizophrenia", the main symptoms of which were extreme inhibition, inability to converse with others, particularly women, and undefined ideas of reference and the feeling that people were laughing at him. He was apt to spend a considerable amount of time standing awkwardly on the edge of groups of fellow students unable to join in and with his arms stretched out straight and hands clenched. After taking iproniazid he became progressively less inhibited, and his social contacts became more and more self-assured until eventually he tried to pass a cheque for $70,000 in a local hotel, which brought him to public attention before his admission to hospital as an emergency.

He was discharged after eighteen months apparently somewhat improved, but he was readmitted some six months later because he "couldn't talk to women" and would spend hours standing pondering over this problem. On the second admission it was decided to try him on imipramine ('Tofranil') to see whether the dosage of the drug could be adjusted to enable him to converse easily with his fellows and avoid hypomania, but this was not easy. When it was noticed that he was a shade too cheerful the dose was reduced from six tablets daily to three—but too late. Next morning he had written two letters to State senators demanding legislation on the management of mental hospitals, and he had to be withdrawn from his employment in the hospital canteen. He quickly quietened down after withdrawal of the drug and administration of chlorpromazine. A further attempt may be made later, on one tablet a day.

Another patient whose main symptoms seemed to be those of depression quickly had his original paranoid psychosis reactivated by imipramine. On withdrawal of the drug, however, he soon ceased expressing his delusional ideas and a change to nialamide ('Niamid') seemed to remove the depression without provoking the underlying paranoid ideation.

Lincoln State Hospital,
Lincoln, Nebraska. FRANK WINSTON.

A SIMPLE DIAGNOSTIC TEST IN THE STEIN-LEVENTHAL SYNDROME

SIR,—The clinical diagnosis of the Stein-Leventhal syndrome is not easy, and investigation by culdoscopy and/or radiography with retrorectal gas insufflation is trying for patients and cannot be performed in small centres, where it would also be impossible to make difficult hormonal assays. We want to indicate to your readers the practical value of an easy test which, we think, might help in the recognition of the Stein-Leventhal syndrome in those women with hirsutism, conspicuous menstrual disturbances (usually amenorrhœa), occasional sterility, and normal or slightly increased urinary 17-ketosteroids—that is, those cases which could be successfully treated with a wedge resection of the polycystic ovaries.

The test can be performed as follows: (*a*) careful collection of the urine during four consecutive days; (*b*) on the morning and in the evening of the 3rd day the patients receive by intramuscular injection 25 mg. of progesterone in oil; (*c*) assay of the 17-ketosteroids is performed on the mixed urine of days 1-2 and days 3-4.

In normal women the injection of this amount of progesterone never increases urinary 17-ketosteroids. On the other hand, in those women with hirsutism and normal or slightly elevated urinary 17-ketosteroids the same treatment can be followed by two completely different results:

(1) In one group the test is "negative" (the urinary 17-ketosteroids do not increase after the two injections of progesterone), as in normal women: in over 90% of women in this group menstruation is normal.

(2) In another group the test is "positive" (the urinary 17-ketosteroids increase by 2-10 mg. in the 48 hours after the two injections of progesterone); almost all these women have conspicuous menstrual disturbances (usually periods of amenorrhœa).

Since in all the women with hirsutism, conspicuous menstrual disturbances, normal or slightly increased urinary 17-ketosteroids, and a "positive" test, the administration of cortisone has been without effect and we have been able to exclude any other cause of the syndrome, we have supposed that these women might have the Stein-Leventhal syndrome.

1. Keith, M. J. *Amer. J. Psychiat.* 1960, **116**, 745.

Three such women have already been operated on and in each our presumed diagnosis of Stein-Leventhal syndrome was correct. All of them have had good results after wedge resection of the ovaries. Whenever it is impossible to perform more difficult and/or more complicated examinations, we therefore think that an increase of urinary 17-ketosteroids after injection of progesterone (" positive " test) might be sufficient criterion for a diagnosis of Stein-Leventhal syndrome in those women with hirsutism, conspicuous menstrual disturbances, occasional sterility, and normal or slightly elevated urinary 17-ketosteroids.

Medical Clinic of the University of Rome.

V. PATRONO
G. NICOLOSI.

BRONCHOGRAPHY

SIR,—I agree with Dr. Smith and his colleagues (March 5) that a lot of heavy weather is made over bronchography, and their method is simple and effective. An equally simple and quick method is that with the Elaine Field needle, using the cricothyroid route.

This needle is, in effect, a small curved cannula with a short-bevel pointed end and a flush-fitting stylet which is mounted on a handle for ease of insertion. It was originally developed for children, but adult sizes are easily obtainable. After insertion, the cannula is tied in position with tapes, which obviates two snags of the ordinary cricothyroid method —i.e., having to hold the needle carefully so that it stays in the right place, and having to reinsert it if both sides are being done at one session. The proximal end of the cannula is 'Record'-fitting to take the bronchogram syringe, which can be disconnected as soon as the right side has been done, and reconnected to do the left after the first lot of films have been taken.

Premedication is not normally necessary and 1 ml. of 2% lignocaine through the cricothyroid membrane via a no. 12 needle should suffice to anæsthetise the skin and bronchial tree. (A second 1 ml. may be advisable in bronchitic patients with a good deal of sputum.) The method is very satisfactory for outpatients.

Central Lincolnshire Chest Unit, Mint Lane, Lincoln.

J. B. WILKINSON.

AUTOIMMUNE HÆMOLYTIC ANÆMIA WITH ACUTE RENAL FAILURE DUE TO PHENACETIN AND P.A.S.

SIR,—Following the paper in your issue of Jan. 2 by Dr. Barbara MacGibbon and her colleagues, I should like to report another case [1] of sensitivity to P.A.S.

A 50-year-old man had been treated for several years for pulmonary tuberculosis associated with renal diabetes. During 1956 he received 15 intravenous injections of P.A.S. (15 g. daily). The 14th and 15th injections were followed by fever. Two years later 12 injections were given. The last 3 injections were ill tolerated (general malaise, vomiting, and fever). Three months later another injection had to be stopped because of severe shock. At no time were signs of hæmolysis observed (no icterus, no dark urine, no anuria or even oliguria). No immediate hæmorrhagic syndrome developed.

The blood was examined 39 days after the last P.A.S. injection. The serum contained an " allergic " antibody capable of agglutinating all compatible red cells, all leucocytes, and platelets of the same blood, but only in the presence of P.A.S. (0·05 g. per 100 ml. final concentration). The average titre was $^1/_{128}$ for red cells, and $^1/_{16}$ for leucocytes and platelets. The reaction was stronger at 37° C than at 15° C or 4° C. No hæmolysis of normal or trypsinised red cells could be demonstrated with fresh serum or with inactivated serum samples to which fresh human serum had been added as a source of complement, in neutral or acid medium. This antibody was still active after heating at 56° C for 20 minutes, but was destroyed by heating at 70° C for 10 minutes. The reaction was inhibited by E.D.T.A. (disodium sequestrene). The action on platelets could also be demonstrated by the inhibition of clot retraction. The antibody could be absorbed and eluted either on red cells and leucocytes or platelets.

The reaction was equally positive with, instead of P.A.S., 3-amino-sodium salicylate, 5-amino-sodium salicylate, *p*-amino sodium benzoate, sodium salicylate, sodium gentisate, methoxy-2-sodium benzoate, nitro-3-sodium salicylate, and nitro-5-sodium salicylate. It was negative with sodium benzoate, sodium phthalate, *p*-sulpho-sodium salicylate, sodium acetyl salicylate, sodium *p*-amino hippurate, *m*-amino-phenol, and phenacetin.

The antibody was not neutralised by the addition of P.A.S. to the serum nor could it be removed by red cells alone.

This case is remarkable because this strong antibody did not provoke clinical hæmolytic anæmia or a hæmorrhagic syndrome although it was active in both red cells and platelets.

Centre National de Transfusion Sanguine, Paris, 15e.

J. DAUSSET
Y. BERGEROT-BLONDELL.

LUNG CANCER AND TOBACCO MOSAIC VIRUS

SIR,—In the search for carcinogens in tobacco smoke there appears to be little research activity in relation to the presence of active tobacco mosaic virus (T.M.V.) in the finished tobacco as found in cigarettes and pipe tobacco. This virus resists the processes of tobacco manufacture, remains infective for plants,[1] and can be demonstrated serologically in tobacco offal.[2]

As a high-molecular-weight protein, it might not be expected that T.M.V. would be carried through in tobacco smoke, but it would be present for ingestion on contact with tobacco (a frequent occurrence in the cigarette-smoker but less common in the pipe-smoker). The induction of lung cancer by an ingested or not predominantly inhaled agent would also be an explanation of the apparent (but not universal) finding in lung-cancer/smoking statistics that inhalers are no worse off than non-inhalers.[3] In these circumstances the cigarette would really function as a man-made vector, perhaps incorporating the correct chemical and temperature changes for the virus at the same time.

The content of ribonucleic acid (R.N.A.) in T.M.V. is approximately 5%,[4] and it is interesting that the other virus which has been suggested as a possible ætiologic agent in lung cancer (influenza virus) also has its nucleic acid in the R.N.A. form. The fundamental role of the nucleic-acid molecule in cell metabolism, which is the subject of so much current interest, is surely worth studying in relation to the R.N.A. of T.M.V. in tobacco. If T.M.V. is involved in the ætiology of lung cancer, one might consider that, being a plant and not an animal virus, long exposure would be necessary for the incubation of lung cancer.

The fact that many types of plant virus must be eaten regularly without causing apparent ill-effect (from tomatoes, vegetables, &c.) would suggest that T.M.V. may have to be modified to attain pathogenicity for animals. The combustion processes in the cigarette might provide such a media for modifying the T.M.V. and it would be interesting to know whether the R.N.A. is liberated in this way from its protein or whether it is itself modified in the smoking process.

T.M.V. must occupy a unique position in biology as the only virus likely to be brought into contact with man at a time when it is being subjected to a considerable temperature gradient [5 6] near the burning cigarette end, as well as complex chemical processes [7] going on around it or near to it in the burning of tobacco. Many possible changes could occur in the virus and the R.N.A. in the smoking process if one compares the changes in the influenza virus when exposed to heat.[8]

1. Presented to the Société française d'Allergie, Paris, Nov. 17, 1959.

1. Smith, K. M. A Textbook of Plant Virus Diseases; p. 507. London, 1957.
2. Imperial Tobacco Co. Personal communication, 1959.
3. Doll, R., Hill, A. B. *Brit. med. J.* 1950. ii, 739.
4. Smith, K. M. Recent Advances in the Study of Plant Viruses; p. 144. London, 1951.
5. Harlow, E. S. *Science*, 1955, **123**, 226.
6. Greene, C. R. *ibid.* p. 227.
7. Clemo, G. R. *J. R. Soc. Hlth*, 1959, **79**, 74.
8. Burnet, M. Enzyme Antigens and Virus. Cambridge, 1958.

Separation or modification of the protein from the R.N.A. or modification of the virus protein would not seem unlikely in these circumstances. If the virus R.N.A. is involved then what we are asking is how long does it take virus R.N.A. or virus protein, modified perhaps in the smoking process, to upset the normal R.N.A./protein mechanism in the lung cell? Certainly many possible changes in the R.N.A./protein mechanism are possible. Could bronchial mucosa be selectively sensitive to this change?

The experience of tobacco workers [9 10] may not be very relevant to the problem unless they smoke, since the smoker gets much "closer" to the tobacco for ingestion than anyone else, and smoking the virus may be different from working with it.

Other factors seem relevant. The ability of plant viruses to multiply in non-plant tissue, e.g. insects—is known.[11 12] Also the refractoriness (resistance to heat and formaldehyde) of the agent responsible for an animal disease (scrapie in sheep) shows that it is possibly another example of an unidentifiable transmissible agent, apparently more akin to some plant viruses than to animal viruses.[13] An insect virus also contains R.N.A.[14] Viruses involved in human disease have been shown to contain R.N.A. (influenza, poliomyelitis)—i.e., the ability of plant viruses to multiply outside the plant tissues is accepted, the agent of another animal disease seems more to resemble a plant-type virus than an animal-type virus, and R.N.A. is present in virus pathogens of insects and man, particularly in a virus suggested as a possible ætiologic agent in lung cancer (influenza). Finally the D.N.A. changes in the nuclei of influenza virus infected cells have been reported as implicating D.N.A. also in the multiplication of an R.N.A. virus.[15] Similar nuclear and D.N.A. changes in poliomyelitis infected cells have been reported.[16] Perhaps attention should be focused on these two active methods of introducing virus R.N.A. to the human lung.

The effect of injected "labelled" T.M.V. in the mouse has been studied by Erickson et al.,[17] who demonstrated T.M.V. uptake in the mitochondria of liver cells, though they did not show intracellular localisation of the virus particles except within the vacuoles of Kupffer cells. They attribute their failure to demonstrate the T.M.V. in the nuclei to deficiencies in their technique.

This possibility of plant-virus involvement in obscure human disease may seem somewhat remote, but the manner of induction of tumour formation by viruses in plants and animals appears to be similar.[18] That the virus (T.M.V.) is not "like" animal viruses (i.e., is a simpler organism) may be more in support of the theory than against it since we would perhaps anticipate a different R.N.A./protein mechanism which is not quite right for the animal (lung) cell. The recent theory of Commoner [19] on the lengthwise replication of T.M.V. and its apparent dependence on protein participation to do so may be relevant. Neither are we looking for an acute illness; long-term possibilities would have to be considered and a mechanism which did not destroy the lung cell.

The possible pathogenetic role for animals of T.M.V. and other plant viruses in tobacco should be investigated, at least to exclude their possible involvement in cancer of the lung. It would be intriguing if the virus which has probably received more study than any other was concerned in the ætiology of lung cancer.

Bristol. P. W. BOTHWELL.

9. Haag, H. B., Hanmer, H. R. *Industr. Med.* 1957, **26**, 559.
10. Case, R. A. M. *Nature, Lond.* 1958, **181**, 84.
11. Smith, K. M. A Textbook of Plant Virus Diseases; p. 87. London, 1957.
12. Cohen, S. C. *in* Viral and Rickettsial Infections of Man (edited by Rivers and Horsfall). London, 1959.
13. Gordon, W. S. *Vet. Rec.* Dec. 7, 1957, p. 3.
14. Zeros, N. *Nature, Lond.* 1956, **178**, 412.
15. Wolff, H. L. *J. Path. Bact.* 1957, **73**, 337.
16. Tenenbaum, E. *Nature, Lond.* 1957, **180**, 1044.
17. Erickson, J. O., Hensley, T. J., Fields, M., Libby, R. L. *J. Immunol.* 1957, **78**, 94.
18. Huxley, J. Biological Aspects of Cancer. London, 1958.
19. Commoner, B. *Nature, Lond.* 1960, **184**, 1992.

A MEMORIAL TO THE LATE DR. BERNARD JOHNSON

SIR,—The sudden and unexpected death of Bernard Johnson in May, 1959, left the Board of the Faculty of Anæsthetists with a great sense of loss which became more apparent as the scope of the work he undertook on its behalf came to light. Many of the present activities of the Faculty of Anæsthetists were initiated by Bernard Johnson and it was his imagination and persistence which carried them through to completion. These include the establishment of the research department, which was not only his idea but for which he collected the funds almost singlehanded, the Faculty scientific meetings, the provision of lecture courses, and the training of post-graduate students.

Many of his friends have expressed the wish to have an opportunity to contribute to a memorial and a committee has been set up to this end. We hope to collect £6000, and it is proposed that this will be devoted to the foundation of a lecture, the provision of a plaque costing approximately £200 to be placed in the Research Department of Anæsthetics at the Royal College of Surgeons, and to provide for a Faculty adviser in postgraduate studies, a function of the Faculty which was very near to Bernard Johnson's heart.

All those friends and colleagues of Bernard Johnson who would like to be associated with this memorial are invited to send their contributions to the Dean of the Faculty of Anæsthetists, Royal College of Surgeons of England, Lincoln's Inn Fields, London W.C.2. Cheques should be made payable to The Faculty of Anæsthetists.

MILES CLIFFORD
Chairman
GEOFFREY ORGANE
Dean
T. CECIL GRAY
J. B. KINROSS
E. A. PASK
RONALD WOOLMER
Bernard Johnson Memorial Committee.

Faculty of Anæsthetists,
Royal College of Surgeons
of England,
London, W.C.2.

Parliament

The Supplementary Estimate

THE Ministry of Health has asked for a supplementary estimate of just over £23½ million.[1] This, Mr. DEREK WALKER-SMITH explained to the Committee of Ways and Means on March 14, contained three main items. Much the largest was £13·8 million for advances made to hospitals on revenue account; of this over 60% was needed to meet pay increases, including almost £11 million for nurses and midwives which brought their pay into line with the relative rewards enjoyed in the community. This was at once an act of justice and an act of policy, and he made no apology for it, costly as it was.

The second main item, £5,684,000, was for the pharmaceutical services. This was due to an increase in the number of prescriptions and to an increase in their average cost, estimated originally as 6*s.* 8*d.*, but now as about 6*s.* 10½*d.* He had on Jan. 29 sent out a special notice, agreed by the General Medical Services Committee, calling attention to the importance of limiting quantities prescribed. Cost investigation in 1955 had established that profits for unbranded standard drugs were not unreasonable, and there was no reason to suppose that the position had changed since then. For proprietary preparations there was an agreement for price-regulation. This was now in the third year of its trial period, which ended in June, and was being reviewed. There had, over the past few years, been major advances in drugs which

1. *Lancet*, Feb. 13, 1960, p. 395.

flowed from a substantial research programme conducted by the industry at its own expense, estimated at about £5 million last year. He thought that our policy must have regard to the desirability of obtaining drugs for the National Health Service at reasonable prices and of providing conditions favourable to further research and development in the industry. There had been a pilot inquiry into the payment of chemists, and a large-scale inquiry covering a range of nearly 1000 standard drugs was now being made. The results of the first six months of the inquiry had become available on Dec. 1 and, after consultation with chemists, certain price adjustments had now been introduced.

The third main item in the Estimate was £1,600,000 for the purchase of poliomyelitis vaccine. The tragic death of an international footballer had made a more vivid impact on the minds of young people than any medical or ministerial exhortation; and by the end of the year the number of young people accepting vaccination was just under $2^1/_2$ million. $8^1/_2$ million children had also accepted vaccination, and more than $6^1/_2$ million people—children and adults—had had a third injection.

Dr. EDITH SUMMERSKILL was dissatisfied with the rising cost of the pharmaceutical services and reminded the Minister that the Comptroller and Auditor-General shared her dissatisfaction.[2] In 1956 proprietary drugs accounted for 36% of the drug bill. The Minister had not mentioned the present proportion, but she believed that it now stood at 70%. The majority fell into categories classified by the Cohen Committee as not therapeutically superior to standard preparations. Cheaper standard drugs would not only be equally effective, but would not have the unfortunate side-effects of some proprietary drugs which had never had adequate clinical control in this country. A leading article in the *British Medical Journal*[3] drew attention to a drug shown to be carcinogenic in animals, which was still being prescribed to people although it was not being advertised.

The Auditor-General, she continued, was doubtful about the effectiveness of the voluntary price-regulation scheme, on which the Minister still appeared to rely. The revelations at the hearings of the United States Senate Anti-Trust and Monopoly Subcommittee on the price of drugs had shocked public opinion in America, and these firms for the most part had established themselves in Britain and were adopting the same business methods here.

In conclusion she asked if the time had not come to examine the prescribing of the specialists. Some of them were asked by the drug houses, in return for suitable remuneration, to test preparations. It was remarkable how a consultant then became prejudiced in favour of one firm. The drug bill of the hospitals had become so high that it was decided to prescribe only for one month for outpatients and then let the general practitioner continue on E.C.10.

Miss EDITH PITT, parliamentary secretary to the Ministry, said that the drug mentioned in the *B.M.J.* leader was subjected to extensive animal tests and, when it appeared safe, was released for clinical use. Over the past five years an enormous number of patients had been treated in this way, and, apart from a local staining reaction at the site of injection, no side-effects or toxic reactions had been reported. There had been investigations subsequently on animals by other doctors using massive doses—proportionately far higher than those ever likely to be used clinically. In any event, this carcinogenicity in animals would not necessarily occur in man, and it remained simply as a warning. The doctors had been given this warning in the medical Press, so few could be unaware of it. It must be left to the practitioners to assess the benefits and conceivable risks, and to decide for themselves whether to embark on such treatment.

The Ministry's information suggested that, for many of the most important drugs, prices in the United States were about twice as great as those charged in Britain by the American subsidiaries. The American firms of which Dr. Summerskill was so critical helped considerably both in the production of our drugs and in our exports. Through their activities our industry had benefited from the very considerable research efforts in the U.S.A. and Switzerland. Voluntary price regulation had produced a considerable number of price-reductions—about 300—and during the past two years prices of corticosteroids had been reduced by 30% without prompting.

2. See *ibid.* Feb. 6, 1960, p. 343.
3. *Brit. med. J.* March 12, 1960, p. 788.

QUESTION TIME

Doctors' and Dentists' Remuneration

Mr. L. A. PAVITT asked the Minister of Health whether he would fix a date for preliminary general discussions with the medical profession concerning the report of the Royal Commission on Doctors' and Dentists' Remuneration.—Mr. DEREK WALKER-SMITH replied: I am not yet ready to propose a date, but I have informed the profession that the Secretary of State for Scotland and I would wish to have such discussions as soon as the Government have completed their initial study of the report.

National Health Service Superannuation

Mr. G. THOMAS asked the Minister of Health what representations he had received from trade unions concerning his unilateral decision to alter the terms of the National Health Service superannuation scheme.—Mr. WALKER-SMITH replied: I have received representations against the proposal to abolish the payment of interest on contributions returned to those who voluntarily leave National Health Service employment, but not against the proposal that the Exchequer should take responsibility for all but a very small part of the actuarial deficit of £80 million. I am at present considering these representations.

Special Hearing-aids for Children

Mr. S. S. AWBERY asked the Minister if he was aware that children in need of special hearing-aids other than the 'Medresco' are unable to obtain the special types required free under the National Health Service, nor can hospitals supply them to patients nor offer grants towards the cost if purchased privately: and if he would take steps to provide special aids, such as bone conductors, free where necessary on the recommendation of an ear, nose, and throat consultant of a local authority.—Miss EDITH PITT replied: There is in the range of medresco hearing-aids a valve-type bone-conduction aid which is obtainable free on the recommendation of a hospital consultant. Commercial aids are not supplied under the hospital service, but in appropriate circumstances a local education authority may provide them without charge through the school health service.

Artificial Limbs

Mr. L. M. LEVER asked the Minister if he would indicate the improvements in design and fitting of artificial limbs which have accrued from the work of the Department of Research and Experiment at Roehampton since 1947.—Miss PITT replied: As a result of the work of the research department, in conjunction with the manufacturers of artificial limbs, there has been substantial improvement in the fitting, alignment and stability of artificial limbs: new types of sockets, corsets and pylons have been introduced: the use of new materials has been extended: and walking appliances for children have been developed. The design of arms has been improved, and many special arm appliances have been produced. Apart from the work which is done for amputees, appliances for patients with paralysed arms have been developed.

Mr. LEVER asked the Minister the average time now taken for major repairs to artificial limbs at Roehampton. Miss PITT: Between 3 and 4 months. Mr. LEVER asked the Minister the average time now taken to supply an entirely new artificial limb, from the date of first measurement to the date of delivery of the new limb.—Miss PITT: About 98 days.

Cost of Poliomyelitis Vaccination

About £6 million has so far been spent on the purchase of poliomyelitis vaccine for England and Wales and the further cost of supplies for 1960 is estimated at £1·7 million.

Obituary

DOUGLAS JAMES CAMPBELL

F.R.C.P.E., D.P.H.

Dr. D. J. Campbell, consultant venereologist to the Sheffield and district area and lecturer in venereal diseases in the University of Sheffield, died in the Royal Hospital, Sheffield, on March 6. He was 56 years of age.

Douglas Campbell spent much of his early life in Edinburgh. He was educated at George Watson's College and the School of Medicine in Edinburgh. He was a licentiate in dental surgery but he never practised dentistry, and he qualified L.R.C.P.E. in 1927. After holding house-physician and house-surgeon posts at the Royal Infirmary, he became senior clinical assistant in the department for venereal diseases in the hospital in 1929. He took the D.P.H. in 1931, and between 1932 and 1937 he was V.D. officer and pathologist for Southampton and consultant in V.D. to the Royal Hants and Southampton Hospital. In 1937 he became consultant venereologist to the city of Lincoln and Holland County Council, V.D. officer and pathologist to Grimsby County Council, and venereologist and dermatologist to the Grimsby Hospitals. From 1939 to 1944 he served as a specialist at headquarters of the Aldershot and South-Eastern Commands and at the Connaught Military Hospital, Aldershot. He also served overseas as adviser in venereology to Allied Forces Headquarters, North Africa, and to 21 Army Group of the British Liberation Army. He held the rank of lieut.-colonel and was awarded the territorial decoration.

After the war he returned to Grimsby, and when the National Health Service was started he became consultant venereologist and moved in 1949 to take charge of the V.D. departments and clinics in the Sheffield district. He was appointed lecturer and clinical teacher in 1950.

C. H. S.-H. writes:

"Campbell's early days in Sheffield were hampered by inadequate premises, lack of beds, and at first difficulties in obtaining enough clinical material for the instruction of undergraduates. He set to work with zeal, however, and built up a first-class service for the treatment of patients and for teaching. Perhaps it was the feeling that the worthwhileness of his medical work was not always recognised that led him to pursue many activities outside medicine. Thus he was a keen rotarian and member of the Edinburgh University association in Sheffield. He was a governor of Epsom College. He was also a member of the Central Consultants and Specialists Committee of the British Medical Association. His status in his own specialty was recognised by his presidency of the Medical Society for the Study of Venereal Diseases."

Dr. Campbell leaves a widow and two sons.

JOHN RODERICK BULMAN

M.B. Edin.

Dr. Bulman, who died in the General Hospital, Hereford, on Feb. 17, was the senior general practitioner of the city.

He was born in Kelso in 1886 and qualified from the University of Edinburgh in 1913. After holding a house-appointment in Edinburgh Royal Infirmary he served throughout the war in the R.A.M.C. On demobilisation he joined the late Dr. Thompson of Hereford in partnership. He retired two years ago. He leaves a widow, four sons, and a daughter.

H. W.-S. writes: "At the end of the late war, Dr. Bulman was instrumental in reviving the almost moribund Hereford Medical Society which is now a flourishing institution, and last year the members presented him with a silver salver. For some years he was also a member of the Hereford city council. His vigorous and kindly personality attracted a host of friends and he was held in universal honour and esteem."

Dr. S. A. HENRY

T. L. D. writes:

"Your obituary notice of S. A. Henry, which so sensitively conveys his terrier-like powers, both the delight and despair of his friends, omits any reference to Sir Thomas Legge's book *Industrial Maladies*. Though this book was possibly in draft before Legge's death, Henry's contribution in seeing it through the press was undoubtedly big. Legge was a great man and Henry an inspired admirer. Whatever was the contribution of each, the result was a medical classic. To mention Henry's share does not detract from Legge's greatness. On the fly-leaf of the book is a quotation ascribed to Thomas Fuller: 'He who cures a disease may be the skillfullest, but he who prevents it is the safest physician'. Some years ago, having failed to trace the quotation in the writings of either of the two Thomas Fullers, I wrote to Henry to ask him the source. For once it seemed that Henry's terrier-like qualities were beaten, and he had to admit that he did not know. I have often wondered whether the quotation (so perfect a description of preventive medicine) might not have had its origin with Legge or Henry. If any reader can trace the quotation I am sure no-one would be more delighted than Henry."

Diary of the Week

MARCH 20 TO 26

Monday, 21st

HUNTERIAN SOCIETY
8.30 P.M. (Talbot Restaurant, London Wall, E.C.2.) Air Commodore W. K. Stewart, Squadron-Leader Peter Howard: Medical Hazards of Space Travel.

Tuesday, 22nd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine*. Prof. J. Waldenström (Malmö), Dr. A. S. McFarlane, Dr. George Discombe: Diseases Associated with Abnormal Plasma Proteins.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Michael Feiwel: Hirsutism.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *History of Medicine*. Sir Gordon Gordon-Taylor: The Long Liston and the Fergusson Speculum.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. Honor Smith: Intrathecal Tuberculin in Disseminated Sclerosis.

Wednesday, 23rd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. H. H. Eddey: Surgery in Cancer of the Mouth. (Hunterian lecture.)

ROYAL SOCIETY OF MEDICINE
5 P.M. *Endocrinology*. Prof. A. L. Loubatières (Montpellier), Dr. J. M. Malins, Dr. J. D. N. Nabarro, Dr. R. S. Walker, Dr. J. M. Stowers: Oral Hypoglycæmic Agents in the Treatment of Diabetes Mellitus.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. RIDDELL: Immunological Aspects of Fungous Disease.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. J. L. Livingstone: Steroids in Asthma.

EUGENICS SOCIETY
5.30 P.M. (Royal Society, Burlington House, Piccadilly, W.1.) Prof. J. F. Danielli: New Life in Old Bodies.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) *Medicine*. Prof. P. R. Allison: Observations of the Pulmonary Circulation in Medical and Surgical Practice.

Thursday, 24th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. A. G. Stansfeld: Necrotising Arteritis. (Erasmus Wilson demonstration.)

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Hospital, Oxford
8.30 P.M. Dr. R. Nassim: Differential Diagnosis of the Porotic Spine.

Friday, 25th

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Obstetrics & Gynæcology*. Prof. J. J. Snoeck (Brussels), Mr. J. A. Chalmers, Mr. G. T. Smedley: The Vacuum Extractor—an Alternative to the Obstetric Forceps.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Mr. E. J. Radley Smith: Brain Abscess.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5
5.30 P.M. Dr. G. K. Stürup (Copenhagen): Treatment of Criminal Psychopaths.

ASSOCIATION OF INDUSTRIAL MEDICAL OFFICERS
10 A.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Opening of two-day meeting.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, W.1
7.30 P.M. Dr. R. R. Willcox: Gonorrhœa and Infectious Venereal Disease in Great Britain.

Notes and News

STERILE SUPPLIES IN HOSPITAL

FOR some years the Sunderland Royal Infirmary has made studies on routine surgical dressings and minor surgical procedures in its medical and surgical wards, its theatres, and its outpatient departments. With the publication of the Nuffield Provincial Hospitals Trust's report [1] on sterilisation practice in six hospitals, and others such as that of Darmady et al.,[2] this work received new emphasis. A team consisting of the group pathologist, two surgeons, and four ward sisters collaborated to set up a central sterilisation service for four wards—three medical and one surgical. This service has been limited in its resources but has already proved its worth by showing that ward sterilisers become unnecessary, that routine dressing of wounds and preparation of trolleys for such procedures as lumbar puncture can be simplified, and that the time taken over these nursing practices can be materially shortened. The impression has been gained that secondary contamination of surgical wounds has been significantly reduced.

The central supply service has approached its task with the attitude: " You tell us what you need, and we will provide it." The system has proved acceptable in practice and has led to a standardisation of technique which has its economic appeal. It is intended to extend it to the other wards, and to such parts of the theatre work, and casualty department and outpatient clinics, as are likely to profit from it. This raises many more administrative and logistic problems than have been met in the pilot scheme.

The Nuffield Provincial Hospitals Trust has shown its interest not only by providing the advice and experience of its working party on hospital sterilisation but also by a grant [3] of £10,000 towards improving the accommodation and increasing the equipment.

PART-TIME RESEARCH

MUCH has been said about the need for posts enabling a consultant in the National Health Service to divide his time between research and hospital practice; and a few such posts have been created. To encourage this combination of clinical work with investigation, the Royal College of Physicians of London is now advertising some of its research fellowships in such a way that they could be held by part-time consultants. In our advertisement columns this week it invites applications for a Joseph Senior White fellowship, which might be extended up to five years.

THE STUDENT AND THE CURRICULUM

THE British Medical Students' Association has published reports on the teaching of social medicine and of psychiatry and psychological medicine.[4] Both reports were prepared by Dr. Roderick MacSween, who was education officer of the Association in 1958–59.

The Association recommends that in all medical schools the students' curriculum should include a course on *social medicine* which should cover aspects of immediate concern to the newly qualified doctor, such as medical sociology, epidemiology, health administration, and the health and welfare services. Visits to factories, kitchens, special clinics, and patients' homes should be included. The importance of disease, not only to the individual but to the community as a whole should be stressed. The Association would not like to see social medicine included as a subject in the final examination, but suggests that a combined examination in social medicine and infectious diseases might be part of a professional examination.

In the report on *psychiatry and psychological medicine* the Association recommends that normal psychology should be taught alongside the preclinical course in anatomy and physiology. Psychiatry should form an integral part of the clinical course in medicine. Students should spend more time at outpatient clinics and on ward-rounds in mental hospitals and units. The emphasis should be on the commonest mental disorders in general practice and in general hospital wards. The Association would like to see the student taught some psychotherapy, and residence or a period of clinical clerking should be compulsory. An examination in psychology should become an obligatory part of the 2nd M.B. in physiology, and an examination in psychiatry of the final examination in medicine. Psychiatrists should be included among the examiners in the final examination in medicine. Many of these recommendations are embodied in the course in psychology and psychiatry lately introduced at Sheffield University.

1. Nuffield Provincial Hospitals Trust. Sterilisation Practice in Six Hospitals. 1958.
2. Darmady, E. M., Hughes, K. E. A., Jones, J. D., Verdon, P. *Lancet*, 1959, i, 622.
3. *Times*, March 7, 1960.
4. Obtainable from the B.M.S.A., B.M.A. House Tavistock Square, London, W.C.1.

University of Cambridge

On March 5 the following degrees were conferred:

M.D.—A. G. Ackerley, J. C. Barker.
M.Chir.—*I. S. M. Jones.
M.B.—*N. A. Atalla, *P. J. F. Baskett, *Simon Harcourt-Webster.
* By proxy.

University of Aberdeen

The honorary degree of LL.D. is to be conferred on Lady Baird, chairman of the North-Eastern Regional Hospital Board, Sir David Campbell, regius professor of materia medica at the University, and Dr. R. S. Aitken, vice-chancellor of the University of Birmingham.

Royal College of Physicians of London

Dr. D. Evan Bedford will give the Lumleian lectures on Tuesday and Thursday, April 5 and 7, at 5 P.M. at the college, Pall Mall East, S.W.1. He will speak on disorders of the pulmonary circulation.

Royal College of Surgeons of England

Faculty of Anæsthetists.—The following have been elected to the Board of Faculty:

Dr. M. D. Nosworthy, Dr. J. A. Lee, Dr. G. Jackson Rees, Dr. W. D. Wylie, representing the fellows; Dr. R. V. Sturton, representing the members.

A diploma of fellowship has been granted to I. M. Hallack.

British Medical Association

The annual meeting is to be held in New Zealand next year, and Mr. Douglas Robb, surgeon to the Greenlane Hospital, Auckland, and pro-chancellor of the University of Auckland, has been elected president of the Association for 1961-62.

Research on Bone Sarcoma

The Medical Research Council invite applications for a Nathan research fellowship for the evaluation of different forms of therapy in bone sarcoma. Further particulars will be found in our advertisement columns.

Medical Administration

The Nuffield Provincial Hospitals Trust is offering six grants (of £500 each) to medical or non-medical graduates who wish to take the course for the diploma in medical services administration in the University of Edinburgh. Further particulars will be found in our advertisement columns.

Refresher Course in Psychological Medicine

Eleven weekly lecture-seminars for general practitioners have been arranged under the auspices of the British Postgraduate Medical Federation by the department of psychological medicine at the Royal Free Hospital. The course will start on April 27 or 28. Further particulars may be had from Dr. S. W. Hardwick, Royal Free Hospital, Gray's Inn Road, London, W.C.1.

Human Relationships in the Care of Mother and Baby

A conference on this subject will be held by the Royal College of Midwives from March 28 to April 1, at St. Anne's College, Oxford. The speakers will include Sir John Charles, Dr. Eleanor Mears, Dr. P. E. Polani, Dr. John Apley, Dr. D. L. Kerr, Dr. David Morris, Mr. P. J. Huntingford, Mrs. C. L. Beynon, Dr. Mavis Gunther, Dr. S. A. MacKeith, Dr. A. K. Graf, Dr. T. E. Oppé, and Dr. M. E. T. Mackenzie. Further particulars may be had from the education office of the college, 15, Mansfield Street, London, W.1.

International Congress on Proctology

This conference will be held in Rome on May 13 and 14. Further particulars may be had from the executive secretary, Dr. G. B. E. Simonetti, Via S. Raffaele 3, Milan, Italy.

International Congress of Internal Medicine

This congress will be held from Aug. 24 to 27, in Basle. The principal subjects of the congress will be pathogenesis and treatment of œdema and clinical uses of enzymes. Further particulars may be had from the secretary of the congress, Prof. H. Ludwig, Steinentorstrasse 13, Basle 10, Switzerland.

Institution of Hospital Engineers

On Saturday, April 9, at 2.30 P.M. at Westminster Medical School, Horseferry Road, London, S.W.1, Dr. L. R. West will give the Sandford Premium lecture. His subject will be engineering principles in medicine.

Institute of Accident Surgery

On Monday, April 25, at 5.30 P.M., in the department of anatomy of the University of Birmingham, Lieut.-General Sir Alexander Drummond, director-general of Army Medical Services, will give the inaugural Ruscoe Clarke lecture. He will speak on the care of the injured.

Hospital Board Chairmen

The Minister of Health has made the following new appointments of chairmen of hospital boards:

Royal Hospital of St. Bartholomew, Mr. M. W. Perrin, F.R.I.C.; The London Hospital, Mr. H. R. Moore; and Hospitals for Diseases of the Chest, London, Sir Reginald Wilson.

Consultants' Retirement and Ages

Of the 147 consultants who retired during 1958–59 on reaching the age-limit, 29 had an A award, 19 a B award, and 33 a C award. Of the 2097 consultants employed (at July, 1959) by boards of governors of teaching hospitals, 1007 were aged fifty or over.

First International Symposium of Cybernetic Medicine

This symposium will be held in Naples, from Oct. 2 to 4, under the presidency of Prof. Aldo Masturzo. The general theme of the symposium will be cybernetic methods in modern medicine. Further particulars may be had from the secretary, Prof. Renato Vinciguerra, Via Roma 348, Naples, Italy.

Anglo-French Medical Exchange Bursaries

Further awards will be made in May to young British medical men engaged in clinical or experimental medicine or in biological research.

The bursaries, offered by the Institut National d'Hygiène, are tenable at any hospital or research institute in France. The value of the grants is 870 N.F. (about £63) a month, tax free. They are normally made for 2-4 months. Application forms can be had from the director, Ciba Foundation, 41, Portland Place, London, W.1. The closing date for application is April 21.

Conference on Industrial Health

The Industrial Welfare Society and the Advisory Council on Occupational Health will hold a conference at B.M.A. Scottish House, 7, Drumsheugh Gardens, Edinburgh, 3, on Thursday, March 24, at 10.30 A.M. The subject will be industrial accidents, and the speakers will include Prof. J. H. F. Brotherston, Prof. J. I. P. James, Mr. A. B. Wallace, and Dr. R. I. McCallum. Further particulars may be had from the society, Robert Hyde House, 48, Bryanston Square, London, W.1.

Parents' Consent to Operation

At a meeting on March 14 the Sheffield Regional Hospital Board considered a recommendation (*Times*, March 15) to set up juvenile courts in hospitals when consent for an emergency operation on a juvenile is necessary. An amendment to refer back the proposal was defeated, and the minute containing the recommendation was automatically approved. The National Council for Civil Liberties has protested strongly against the decision and called on the Minister of Health to issue a whitepaper.

The Langley prize has been awarded to Dr. David Scott, epidemiologist in the Medical Service of Ghana, for his paper on the epidemiology of human trypanosomiasis in Ashanti.

Major-General W. A. Robinson has succeeded Major-General A. E. Campbell as deputy director-general of Army Medical Services.

Dr. D. G. Evans, medical officer to Philips Electrical Industries Ltd., has been appointed full-time medical adviser to the Trades Union Congress.

A lecture demonstration for general practitioners will be held on Sunday, April 3, at 10.15 A.M., at University College Hospital, London, W.C.1. Dr. T. A. J. Prankerd will speak on the anæmias.

The Biochemical Society will hold a meeting on Friday, March 25 at 10.30 A.M. at the School of Chemistry, University of Leeds.

The annual general meeting of the members of the Auxiliary Royal Army Medical Corps Funds will be held at 11, Chandos Street, London, W.1, on Monday, April 4, at 5 P.M.

The editorial office of the *Biochemical Journal* will move on March 26 from the Lister Institute. All communications should be addressed to the secretary to the editorial board of the journal, 133–135, Oxford Street, London, W.1.

CORRIGENDA: *Renal Changes in Essential Hypertension.*—In the annotation last week (p. 586) the 5th line of the second paragraph should have ended with the words " cardiovascular derangement ".

More Speed, Less Haste.—In the fourth line from the end of the leading article last week (p. 582) we mentioned Nissen's opinion without including the reference, which is: Nissen, R. *German med. Monthly*, 1959, **4**, 287.

Appointments

BARCLAY, T. L., M.B. Edin., F.R.C.S.E.: part-time consultant in plastic surgery, regional burns unit, Pinderfields General Hospital, Wakefield.
FIRTH, GEORGE, M.B. Leeds, D.P.H.: senior assistant county M.O. and school M.O., Ilkley, Otley, and Wharfedale, Yorkshire.
GODFREY, L. W., M.B. Lond., F.R.C.S.: consultant in traumatic and orthopædic surgery, Aylesbury area hospitals.
OYLER, C. R., M.R.C.S.: assistant M.O.H. and school M.O., Sheffield.
POWELL, H. D. W., M.B. Edin., F.R.C.S.: part-time consultant in traumatic and orthopædic surgery, High Wycombe and Amersham group hospitals accident and orthopædic service.
QUIGLEY, BRIDGET M. A., M.B. N.U.I., D.P.M.: assistant psychiatrist (S.H.M.O.), St. George's Hospital, Morpeth, Northumberland.
TEMPLEMAN, G. H., M.B.E., M.D. Leeds, M.R.C.P.: consultant in chest diseases and medical superintendent, Killingbeck Hospital and Gatesforth Hospital, near Selby, Yorkshire.
WEINBERGER, MAURO, M.D. Genoa, D.M.R.E.: physician-in-charge, Ilford chest clinic.
ZOOB, MAX, M.D. Lond., M.R.C.P.: part-time consultant cardiologist, Preston Hall Hospital, Aylesford, Kent.

The Hospital for Sick Children, Great Ormond Street, London:

CALLAGHAN, R. P., M.B. Lond.: house-surgeon.
DANKS, D. M., M.D. Melb., M.R.A.C.P.: house-physician.
ELDERKIN, F. M., M.B. Durh., M.R.C.P.E., D.C.H.: medical registrar.
HSIA, Y. E., B.M. Oxon., M.R.C.P.: house-physician.
KINSBOURNE, MARCEL, B.M. Oxon., M.R.C.P.: medical registrar.

University College Hospital, London:

FLYNN, F. V., M.D. Lond.: consultant in chemical pathology.
PHILPS, F. R., M.B.E., M.D. Lond.: consultant in exfoliative cytology.
STOKES, JOAN, M.B. Lond., F.R.C.P.: consultant clinical bacteriologist.

Colonial Appointments:

BHEENICK, JEEAN, M.B. Edin., D.T.M. & H., D.A.: specialist (anæsthetics), Mauritius.
CURRIE, J. R., M.R.C.S., D.T.M. & H.: pathologist, Kenya.
EVANS, W. J. M., M.B. Lond., D.P.H.: chief M.O., Tanganyika.
JACKSON, N. J., M.B. Durh.: senior M.O., St. Helena.
JAMES, P. A., M.B. Brist., F.R.C.S.: thoracic surgeon (specialist), Uganda.
KERR, W. G., M.B. Edin., F.R.C.S.E.: senior specialist, Tanganyika.
MOFFAT, E. C., L.R.C.P.E.: M.O., Bahamas.
NUNAN, T. A., M.B. N.U.I.: M.O., Nigeria, Northern Region.
O'HOLOHAN, D. R. M., M.B. N.U.I., M.R.C.P.: M.O., North Borneo.
ROBINSON, M. R. G., M.B. Lond., D.OBST.: M.O., Nigeria, Northern Region.
SHARPE, R. A., M.B. Brist.: M.O., Bahamas.
SHINE, I. B., M.B. Cantab.: M.O., St. Helena.
TITMAS, J. M., M.B. Lond.: M.O., Hong Kong.
WILKEY, A. O., F.R.C.S.: specialist (surgeon), Federation of Nigeria.

Births, Marriages, and Deaths

BIRTHS

PALFREY.—On Sunday, Feb. 28, to Ann (née Hewetson) and John Palfrey, a son, David Keith—a brother for Michael, Susan, and Christopher.
WILKINSON.—On March 11, to Clodagh, wife of Dr. J. B. Wilkinson, of 3, Greestone Place, Lincoln, a son.